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NEW ENGLAND POSTGRADUATE ASSEMBLY
November 2-4, 1953

Announcement on Page iv

# The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 249 OCTOBER 15, 1953 NUMBER 16

**Observations on the Use of Cortisone and ACTH in Rheumatoid Arthritis** . . . . 635
*William S. Clark, Henrick O. Tonning, J. Peter Kulka and Walter Bauer*

**Modern Concepts in the Treatment of Otitis Media** . . . . . 643
*Bernard Zonderman*

**An Approach to the "Skid Row" Problem in Boston** . . . . . 646
*David J. Myerson*

**Medical Progress: Enzymes in Clinical Medicine: Recent Developments in the Practical Application of Enzymes to Clinical Medicine** . . . . . 650
*Henry J. Tagnon*

**Massachusetts Medical Society** . . . . . 669
**Correspondence** . . . . . 670
**Book Reviews** . . . . . 670

**Medical Intelligence: Mid-Thigh Amputation in a Patient with Hemophilia** . . . . . 657
*John H. Crandon, Leonard Staudinger, Jr., and Eli Friedman*

**Case Records of the Massachusetts General Hospital** . . . . . 659

**Editorials:**

*Water-Pollution Control* . . . . . 667
*Medical Schools at Midcentury* . . . . . 667
*Otitis Media and Myringotomy* . . . . . 668
*Twelfth Postgraduate Assembly* . . . . . 669

**Books Received** . . . . . 671
**Nonclinical Notes** . . . . . 672
**Notices** . . . . . 672

Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879.
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By the Staff of the Institute for Sex Research at Indiana University. Alfred C. Kinsey, Wardell B. Pomeroy, Clyde E. Martin, Paul H. Gebhard, Research Associates; and Jean M. Brown, Cornelia V. Christenson, Dorothy Collins, Ritchie G. Davis, William Dellenback, Alice W. Field, Hedwig G. Leser, Henry H. Remak, Eleanor L. Roehr. Consultants for all or for specialized parts of the book: Jerome Cornfield, Harold Dorn, Robert Laidlaw, Karl Lashley, Emily Mudd. 842 pages, 6" x 9". 151 charts; 179 tables; 4 illustrations. $8.00.

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The Journal of the American Chemical S

VOL. 50 FEBRUARY, 1928

# A QUARTER OF A

# 1928

[Contribution from the Research Laboratories of Parke, Davis and Co.]

## THE ACTIVE PRINCIPLES OF THE POSTERIOR LOBE OF THE PITUITARY GLAND.[1] I. THE DEMONSTRATION OF THE PRESENCE OF TWO ACTIVE PRINCIPLES. II. THE SEPARATION OF THE TWO PRINCIPLES AND THEIR CONCENTRATION IN THE FORM OF POTENT SOLID PREPARATIONS

By Oliver Kamm, T. B. Aldrich, J. W. Grote, L. W. Rowe and E. P. Bugbee

Received December 31, 1927 Published February 4, 1928

### Introduction

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## HOTEL STATLER, BOSTON—NOVEMBER 2-4

## *Program*

### MONDAY, NOVEMBER 2, 1953

MORNING SESSION

MOTION PICTURES — *Georgian Room*

8:30 Observation of Human Ovulation by the Pelviscope.
DR. JOSEPH B. DOYLE, Boston City Hospital.

*Ball Room Assembly*

8:30 Some Aspects of Accessible Cancers — Skin.
Ministry of Health of London and Royal Cancer Hospital.

SYMPOSIA — *Georgian Room*

9:15 (1) Accidents in Children.
DR. R. CANNON ELEY, Moderator

*Ball Room Assembly*

9:15 (2) Surgery in the Aged.
DR. LELAND S. MCKITTRICK, Moderator

10:15 RECESS *Visit the Exhibits*

LECTURES — *Georgian Room*

10:45 Anesthesia Including Local.
DR. EMANUEL M. PAPPER, New York, N. Y.

11:30 Hand Trauma.
DR. J. EDWARD FLYNN

LUNCHEON PANELS — *No. 1 — Parlor A*

12:30 Problems in GU Surgery.
DR. WYLAND F. LEADBETTER, Moderator

*No. 2 — Parlors B and C*

12:30 Infectious Hepatitis.
DR. PERRY J. CULVER, Moderator

2:15 RECESS *Visit the Exhibits*

AFTERNOON SESSION

LECTURES — *Georgian Room*

2:30 Management of Anuria.
DR. MAURICE B. STRAUSS

3:30 RECESS *Visit the Exhibits*

4:00 Surgery of Ambulatory Patients.
DR. L. KRAEER FERGUSON, Philadelphia, Pa.

---

### TUESDAY, NOVEMBER 3, 1953

MORNING SESSION

MOTION PICTURES — *Georgian Room*

8:30 Radioisotopes — Their Application to Humans.
(Medical Film Guild)

*Ball Room Assembly*

8:30 Overdependency.
Mental Health Division of the Department of National Health and Welfare — National Film Board of Canada.

SYMPOSIA — *Georgian Room*

9:15 (1) Treatment of Common Skin Conditions.
DR. WILLIAM R. HILL, Moderator

*Ball Room Assembly*

9:15 (2) Management of Urinary Tract Infections.
DR. MAXWELL FINLAND, DR. J. HARTWELL HARRISON

10:15 RECESS *Visit the Exhibits*

LECTURES — *Georgian Room*

10:45 Drug Therapy for Pain.
DR. HENRY K. BEECHER

11:30 Complications of and Contraindications to the Use of ACTH and Cortisone.
DR. CHARLES RAGAN, New York, N. Y.

LUNCHEON PANELS — *No. 3 — Parlor A*

12:30 Use of Drugs in the Management of Hypertension.
DR. ROBERT W. WILKINS, Moderator

*No. 4 — Parlors B and C*

12:30 Fractures in General Practice.
DR. EDWIN P. CAVE, Moderator

2:15 RECESS *Visit the Exhibits*

AFTERNOON SESSION

LECTURES — *Georgian Room*

2:30 The Use of Chemotherapeutic and Antibiotic Drugs in the Treatment of Acute Respiratory Infections.
(a) In Children.
DR. LEWIS L. CORIELL, Camden, N. J.
(b) In Adults.
DR. LOUIS WEINSTEIN

3:45 RECESS *Visit the Exhibits*

4:15 Modern Pharmacopoeia for Heart Disease.
DR. EUGENE H. DRAKE, Portland, Maine

EVENING SESSION

JAMBOREE — *Georgian Room*

8:15 HAROLD G. HOFFMAN, former Governor of New Jersey.

9:15 Entertainment. The Tuckers, telepathists.

---

### WEDNESDAY, NOVEMBER 4, 1953

MORNING SESSION

MOTION PICTURES — *Georgian Room*

8:30 Sigmoid, Rectal and Anal Canal — Endoscopic Views.
DR. J. P. NESSELROD
Northwestern University Medical School

*Ball Room Assembly*

8:30 Cancer: The Problem of Early Diagnosis.
American Cancer Society and National Cancer Institute.

SYMPOSIA — *Georgian Room*

9:15 (1) Tonsillectomy — Yes or No.
DR. JAMES MARVIN BATY, Moderator

*Ball Room Assembly*

9:15 Migraine.
DR. JOHN R. GRAHAM, Moderator

10:15 RECESS *Visit the Exhibits*

LECTURES — *Georgian Room*

10:45 Medical Management of Tuberculosis.
DR. GORDON M. MEADE, Saranac Lake, N. Y.

11:30 Surgical Management of Tuberculosis.
DR. HERBERT C. MAIER, New York, N. Y.

LUNCHEON PANELS — *No. 5 — Parlor A*

12:15 Management of Chronic Non-Tuberculous Pulmonary Infection.
DR. THEODORE L. BADGER, Moderator

*No 6 — Parlors B and C*

12:15 Tumors of the Breast.
DR. IRA T. NATHANSON, Moderator

2:00 RECESS *Visit the Exhibits*

AFTERNOON SESSION

LECTURES — *Georgian Room*

2:30 Management of an Allergic Child.
DR. JEROME GLASER, Rochester, N. Y.

3:00 Management of Progressive Asthma.
DR. BRAM ROSE, Montreal, Canada.

3:30 RECESS *Visit the Exhibits*

3:45 Clinicopathological Conference.
DR. BENJAMIN CASTLEMAN
DR. FRANZ J. INGELFINGER

*Assembly Adjourned*
FRANK P. FOSTER, M.D., General Chairman
CHARLES S. DAVIDSON, M.D., Chairman
Program Committee

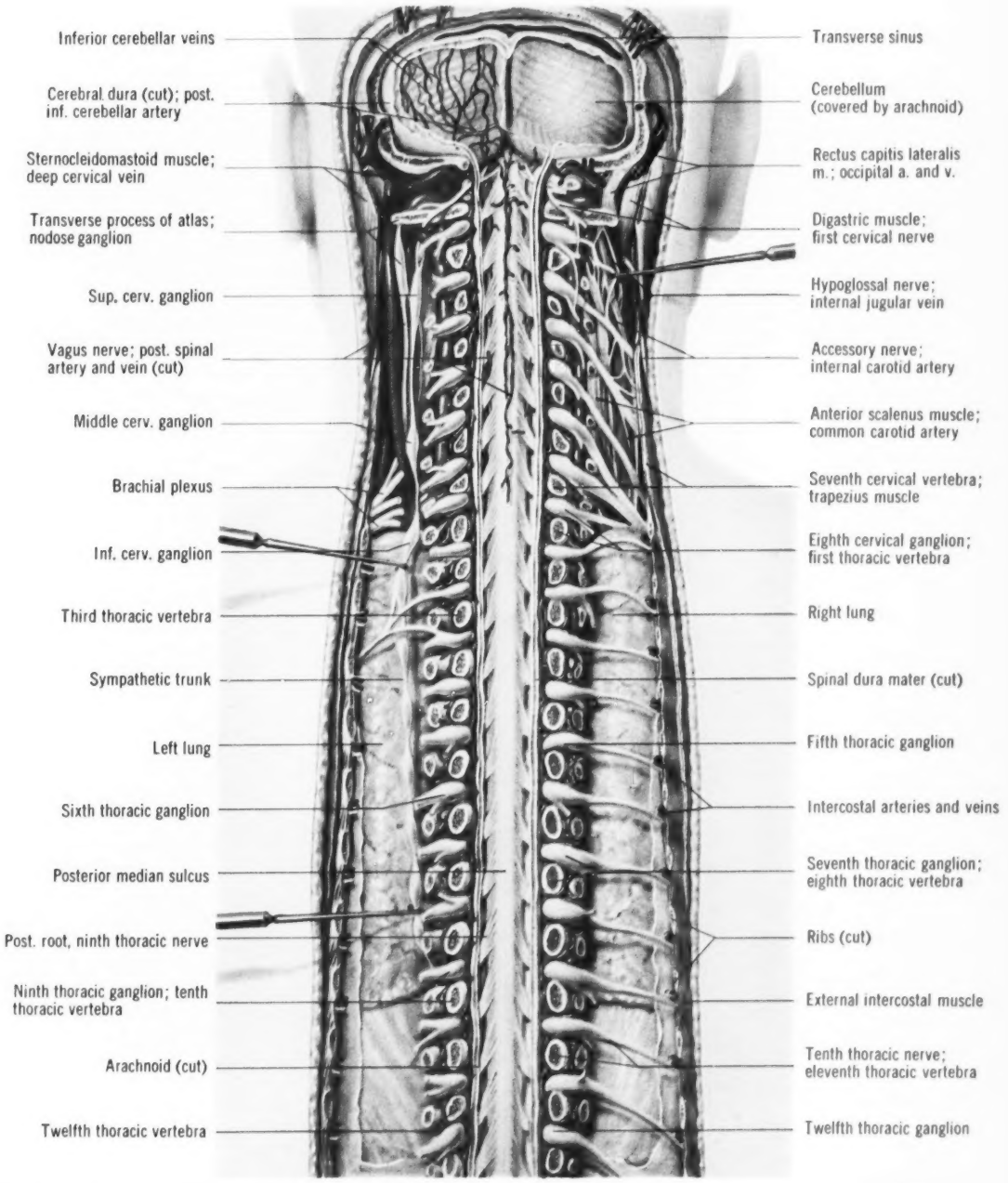
Definitely scheduled meetings are:

NEW ENGLAND DIABETES ASSOCIATION. Monday, November 2, 8:15 p.m. Auditorium, Beth Israel Hospital.

NEW ENGLAND CARDIOVASCULAR SOCIETY. Monday, November 2, 8:00 p.m. Morse Auditorium, Museum of Science, Science Park, Boston.

COUNCIL OF THE NEW ENGLAND STATE MEDICAL SOCIETIES. Tuesday, November 3, 4:00 p.m. Hotel Statler, Parlor A.

# Cervical *and* Thoracic Regions *of the* Spinal Cord


Inferior cerebellar veins
Cerebral dura (cut); post. inf. cerebellar artery
Sternocleidomastoid muscle; deep cervical vein
Transverse process of atlas; nodose ganglion
Sup. cerv. ganglion
Vagus nerve; post. spinal artery and vein (cut)
Middle cerv. ganglion
Brachial plexus
Inf. cerv. ganglion
Third thoracic vertebra
Sympathetic trunk
Left lung
Sixth thoracic ganglion
Posterior median sulcus
Post. root, ninth thoracic nerve
Ninth thoracic ganglion; tenth thoracic vertebra
Arachnoid (cut)
Twelfth thoracic vertebra
Transverse sinus
Cerebellum (covered by arachnoid)
Rectus capitis lateralis m.; occipital a. and v.
Digastric muscle; first cervical nerve
Hypoglossal nerve; internal jugular vein
Accessory nerve; internal carotid artery
Anterior scalenus muscle; common carotid artery
Seventh cervical vertebra; trapezius muscle
Eighth cervical ganglion; first thoracic vertebra
Right lung
Spinal dura mater (cut)
Fifth thoracic ganglion
Intercostal arteries and veins
Seventh thoracic ganglion; eighth thoracic vertebra
Ribs (cut)
External intercostal muscle
Tenth thoracic nerve; eleventh thoracic vertebra
Twelfth thoracic ganglion

*This is one of a series of paintings for Lederle by Paul Peck, illustrating the anatomy of various organs and tissues of the body which are frequently attacked by infection, where aureomycin may prove useful.*

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*Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Company, 1952, p. 172.

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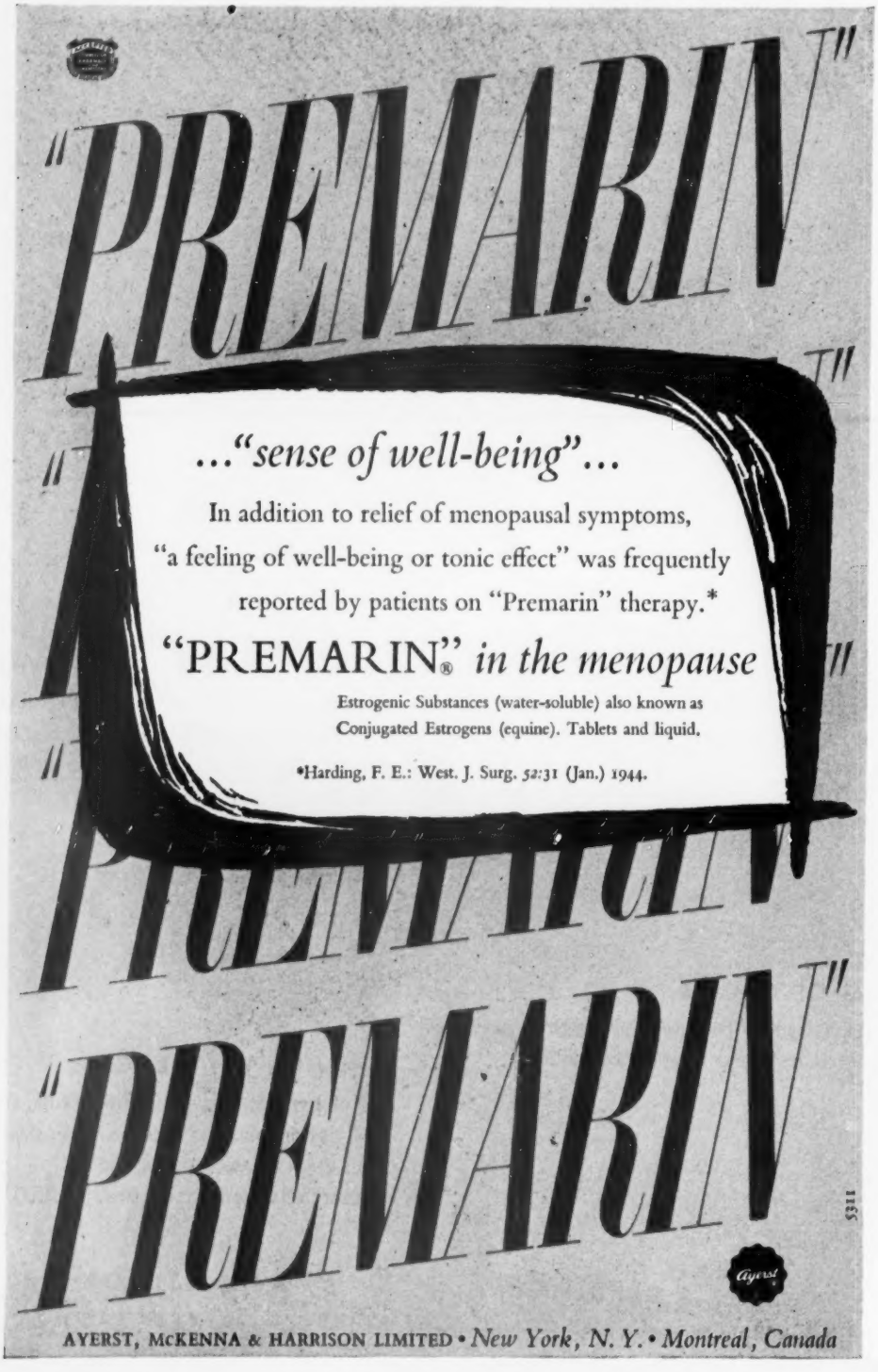
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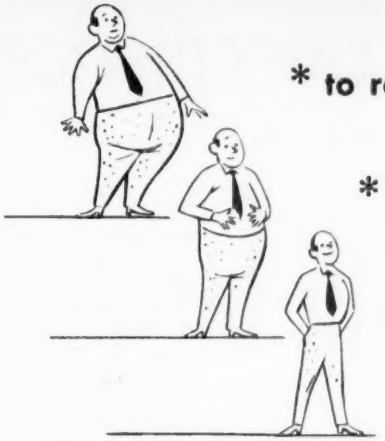

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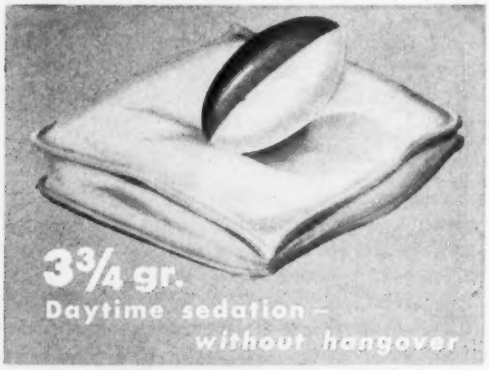

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"Upstairs, the room was real clean, the bed comfortable and I slept like a log. Came down in the morning—still no clerk. So I left three dollars at the desk and went on. Can you imagine folks that trustful?"

*From where I sit, running a hotel on the honor system shows a real trust in people. And people always appreciate being trusted. Letting the other fellow follow his profession without interference is one way of trusting your fellow citizens. So is your regard of* my *liking an occasional glass of beer. You may prefer buttermilk, but let's hope neither of us "register" a complaint against the other.*

Joe Marsh

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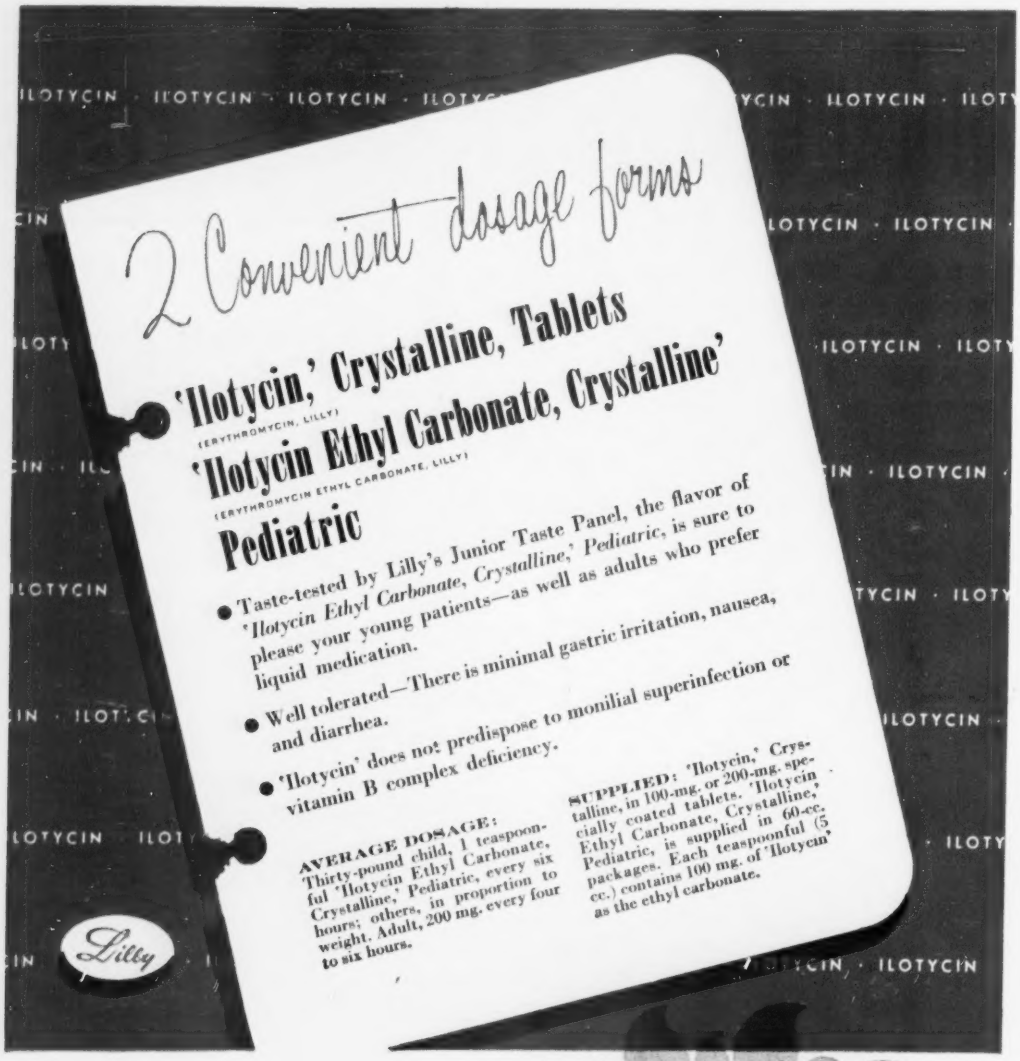
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Journal of Medicine

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Volume 249 OCTOBER 15, 1953 Number 16

# OBSERVATIONS ON THE USE OF CORTISONE AND ACTH IN RHEUMATOID ARTHRITIS*

WILLIAM S. CLARK, M.D.,† HENRICK O. TONNING, M.D.,‡ J. PETER KULKA, M.D.,§ AND WALTER BAUER, M.D.¶

BOSTON

CORTISONE and ACTH have favorable effects on the clinical, laboratory and histologic manifestations of rheumatoid arthritis. However, neither of these agents is curative or specific, and both are capable of inducing the disturbing biochemical and pathologic changes of Cushing's syndrome.[1-7] It is too early to determine their effects on the ultimate course of this unpredictable, chronic disease, but cumulative experience permits certain general conclusions regarding their ameliorative properties. "Improvement" in rheumatoid arthritis embraces a variety of changes in its manifestations, ranging from remissions in articular and systemic inflammatory processes to purely functional or subjective changes. Accordingly, it is difficult to determine categorically the efficacy of any ameliorating agent. A comprehensive approach is obviously necessary in evaluating hormone therapy and defining its margin of safety.

This report describes observations on the use of cortisone and ACTH in 52 patients with rheumatoid arthritis and impressions gained to date concerning their possible place in the therapeutic armamentarium against this disease.

## PROCEDURE

Fifty-two patients (28 males and 24 females), ranging in age from two and a half to sixty-two years, were treated with cortisone (Cortone‖) or ACTH (Acthar**) or both (Fig. 1). Four male patients had spondylitis with involvement of only the hip or the shoulder or both; the remainder had peripheral joint disease. Systemic manifestations included active ocular involvement in 6 cases, aortic insufficiency in 2 and pericarditis in 1. Thirty-four patients received cortisone and 10 ACTH alone; 8 were given both hormones, but on separate occasions. For simplicity of presentation, experiences with each hormone are treated separately. Thus 42 patients received cortisone and 18 patients ACTH, for a total of 60 patients, and these figures are used henceforth.

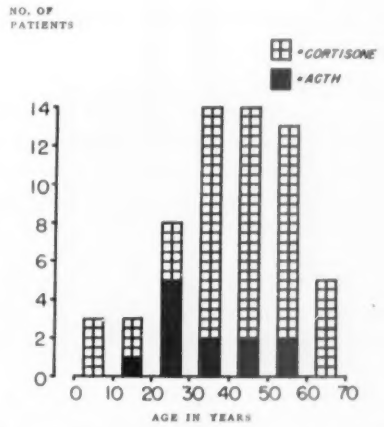


FIGURE 1. *Patients Receiving Cortisone and ACTH (Total of 35 Treatments for Male and 25 Treatments for Female Patients).*

The total duration, including previous attacks, ranged from one to twenty-nine years (Fig. 2). Cortisone was administered to 35, and ACTH to 17 patients experiencing exacerbations of less than three years' duration.

Classification of the stage of the disease by the criteria approved by the American Rheumatism Association[8] is shown graphically in Figure 3.††

*From the departments of Medicine, Massachusetts General Hospital and Harvard Medical School, and the Massachusetts Department of Public Health.

Publication No. 152 of the Robert W. Lovett Memorial for the Study of Crippling Disease, Harvard Medical School.

The expenses of this investigation were defrayed in part by a grant from the Commonwealth Fund.

†Formerly, instructor in medicine, Harvard Medical School, and assistant physician, Massachusetts General Hospital.

‡Formerly, research fellow in medicine, Harvard Medical School, and clinical and research fellow in medicine, Massachusetts General Hospital.

§Formerly, instructor in pathology, Harvard Medical School.

¶Jackson Professor of Clinical Medicine, Harvard Medical School; chief of medical services, Massachusetts General Hospital.

‖Kindly supplied by Merck and Company, Incorporated, Rahway, New Jersey.

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††The stage of the disease concerns the degree of presumably irreversible involvement rather than activity. Stage I is characterized only by subchondral bone atrophy, Stage II by cartilaginous and cortical destruction, Stage III by deformities such as ulnar deviation and subluxation, and Stage IV by fibrous or bony ankylosis. Nodules and significant muscle atrophy must not be present in Stage I.

Twenty-two of the patients receiving cortisone were classified as Stage II, 15 as Stage III, and 5 as Stage IV. Nine cases in which ACTH was used were classified as Stage II, 7 as Stage III, and 2 as Stage IV.

Severity of the disease was estimated from the number of joints involved, the degree of inflammatory activity in these joints, the severity of constitutional symptoms and the rapidity of progression. Four degrees of severity were established (Fig. 4). Of patients receiving cortisone, 1 had mild, 16 moderate, 16 moderately severe, and 9 severe disease.

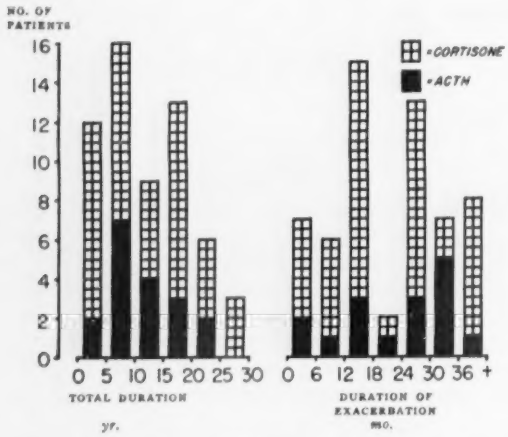


FIGURE 2. *Total Duration of Arthritis, Including Previous Attacks.*

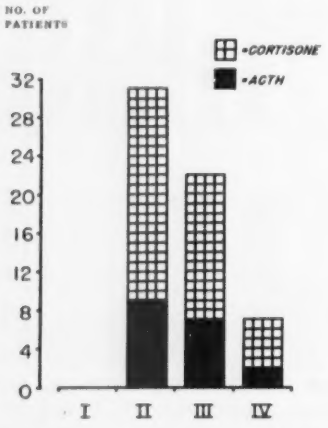


FIGURE 3. *Classification of the Stage of Arthritis (Criteria Approved by American Rheumatism Association).*

Of patients receiving ACTH, 1 had mild, 3 moderate, 10 moderately severe, and 4 severe disease.

Initial doses of cortisone ranged between 12.5 and 300 mg., and maintenance doses between 25 and 200 mg. a day. Only 4 patients received initial doses greater than 200 mg.; 3 received initial doses below 75 mg. Initial doses of ACTH ranged between 40 and 100 mg., and maintenance doses between 40 and 280 mg. a day.* A standard daily dose of 20 to 25 mg. of ACTH was used for intravenous administration.

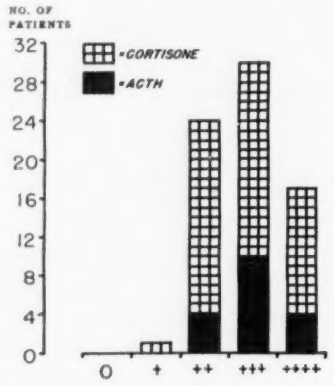


FIGURE 4. *Severity (Activity) before Treatment.*

Cortisone was given chiefly by mouth, usually in two or three daily doses. ACTH was administered intramuscularly in an aqueous or saline solution to 8 patients and in long-acting vehicles to 9. Five patients received ACTH (lyophilized powder) intravenously; 20 to 25 mg. was added to 1.5 liters of 5 per cent dextrose solution and given slowly for a period of eight or more hours. Some patients received two or more different preparations of ACTH.

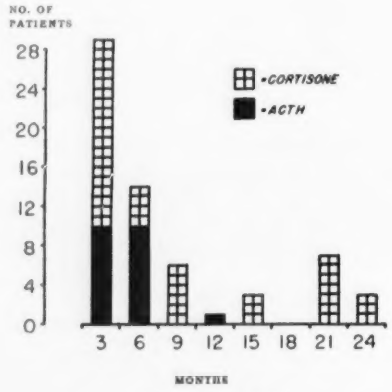


FIGURE 5. *Duration of Therapy.*

*At the time of preparation of this report, only crude ACTH (Armour) had been used. Subsequent experience with purified ACTH (Armour) indicated that maintenance doses of 20 mg. a day were approximately equivalent to 40 to 60 mg. of the less purified material.

The duration of therapy is shown graphically in Figure 5. Six patients received cortisone for less than two weeks, treatment having been discontinued in 2 because of side effects and in the remainder by design. In 2 cases in which ACTH was given for less than two weeks, treatment was discontinued in 1 because of side effects and in the other by design.

At the time this report was prepared, 20 patients continued to receive cortisone, and 2 ACTH.

In the evaluation of results, subjective and objective improvement were treated separately and simply estimated by the degree of change in symptoms and signs during therapy. To determine subjective response, attention was given to pain, aching, stiffness, soreness and freedom of motion. Objective evaluation was based on the palpable evidence of joint inflammation, including effusions, soft-tissue thickening, heat and tenderness, and changes in such systemic manifestations as fever, subcutaneous nodules, ocular involvement and pericarditis when present.

Euphoria, increased appetite and weight gain were considered relatively insignificant in measuring

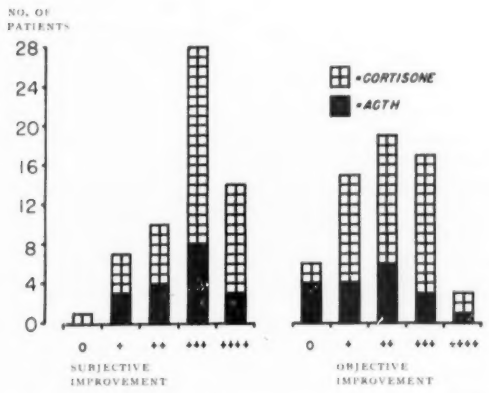


FIGURE 6. *Subjective and Objective Improvement during Therapy.*

activity of the disease. Clinical and functional results were classified by the criteria of the American Rheumatism Association.[8] These specify that an exacerbation in any joint during the period of evaluation classifies that patient as unimproved. Since such exacerbations are frequent on adequate hormone therapy, the criteria were applied during periods of maximal improvement. This, of course, represents a modification of the original recommendations. Histologic studies were performed on joint specimens and subcutaneous nodules from 4 patients who had been receiving ACTH and 8 who had been receiving cortisone. Sedimentation rates were determined in all but 1 patient by the Rourke–Ernstene[9] method. Synovial fluid was examined before and during therapy by methods described by Ropes and Bauer.[10]

All patients were continued on the previous conservative regimen. This program consisted of twelve to twenty-four hours of rest, aspirin, hot fomentations or hot tub baths, or both, and active exercises to all involved joints. Aspirin was administered to tolerance (usually 3.6 gm. or more daily in adults) until shortly before the start of treatment and subsequently resumed on all patients receiving continuous therapy. Progressive-resistance exercises, removable casts, traction, crutches and psychotherapy were prescribed when indicated.

During hormone remissions the time out of bed was increased slowly in patients on continuous

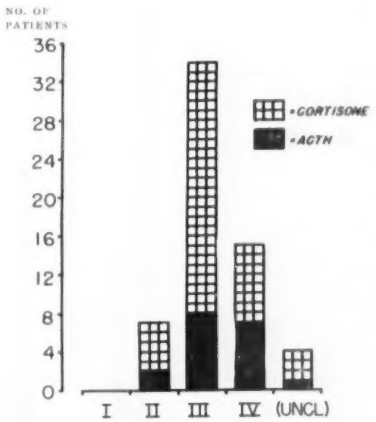


FIGURE 7. *Clinical Results (Modified) According to Criteria of American Rheumatism Association.*

therapy to a maximum of twelve hours a day. The bed-rest routine was difficult to enforce, but all patients were constantly urged to continue it as prescribed.

## CLINICAL RESULTS

Degrees of maximal subjective and objective improvement during therapy are shown graphically in Figure 6. Cortisone induced major subjective improvement (+++ and ++++) in 31 patients (74 per cent) and major objective improvement in 16 (38 per cent). Major subjective improvement occurred in 11 (60 per cent) and major objective improvement in 4 patients (22 per cent) receiving ACTH. Subjective improvement almost always exceeded objective improvement. Only 1 patient receiving cortisone failed to experience subjective improvement, and 2 had no objective improvement. All patients receiving ACTH had subjective improvement, but 4 had no objective improvement.*

*The 4 patients showing no objective improvement received the less purified ACTH in long-acting vehicles, intramuscularly.

Clinical results, classified according to the criteria of the American Rheumatism Association, are shown graphically in Figure 7. By these objective criteria only 5 patients (12 per cent) receiving cortisone and 2 (11 per cent) receiving ACTH had major improvement, whereas 26 (65 per cent) receiving cortisone and 8 (44 per cent) receiving ACTH had minor improvement. Three cases with spondylitis and hip involvement were not classified since these criteria do not apply to patients without peripheral joint involvement.

Functional improvement, graded according to the criteria of the American Rheumatism Association,

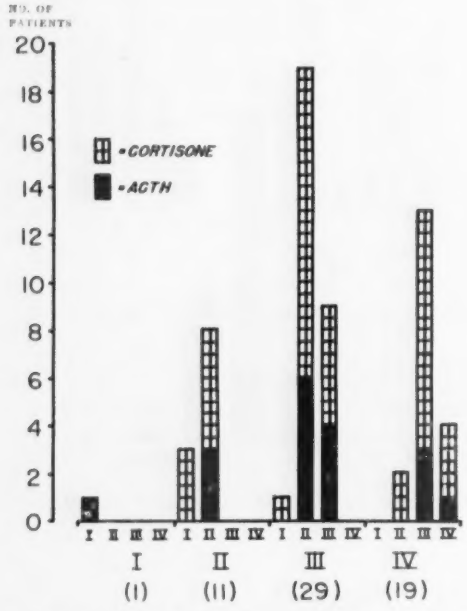


FIGURE 8. *Functional Results (Graded According to Criteria of American Rheumatism Association).*

is shown graphically in Figure 8.* Only 1 patient could be placed in Class I before therapy. Eight patients receiving cortisone started in Class II, and of these, 3 moved into Class I. Of 19 patients receiving cortisone who started in Class III, 1 moved into Class I and 13 into Class II. Fifteen patients receiving cortisone started in Class IV. Of these, 2 moved into Class II and 10 into Class III. Three patients receiving ACTH started in Class II, and their functional status did not change. Of 10 patients receiving ACTH who started in Class III, 6 moved to Class II. Four patients receiving ACTH started in Class IV, and 3 moved to Class III. Six male patients, who were occupationally incapacitated before therapy, were returned to full-time employment on maintenance doses of cortisone. Another patient, unable to maintain full employment because of his disease, was restored to full-time work on maintenance ACTH therapy. Systemic manifestations, including fever when present, generally improved. Nodules frequently decreased in size but did not completely disappear. In 1 case signs of acute pericarditis subsided completely within five days. The murmurs of aortic regurgitation did not change. Ocular inflammation diminished in all patients with the exception of 1 suffering from uveitis and glaucoma, in whom it was necessary to discontinue ACTH because of an increase in intraocular pressure.

Five patients had corrective orthopedic surgery in conjunction with cortisone therapy. A vitallium-cup arthroplasty was performed on 3 patients, and an arthroplasty of the knee on 2. The operative end-results did not seem to be significantly influenced by these agents as compared with results obtained before the advent of hormone therapy.

Cortisone was administered to 1 patient with uveitis before and after a cataract extraction. This operation had previously been unsuccessful in this clinic because of postoperative hemorrhages and exacerbations of the uveitis. The surgical result was excellent, and there were no complications. The patient is still on cortisone after two years. A similar procedure on another patient, who received ACTH, was unsuccessful. Although one eye had been operated upon with a return of some vision, at the time of operation upon the second eye, excessive fluid retention appeared that was unsuccessfully controlled and ultimately necessitated discontinuation of hormone therapy. Intraocular hemorrhage occurred postoperatively, with an exacerbation of the uveitis, and complete loss of vision resulted.

TABLE 1. *Time of Relapse upon Cessation of Therapy.*

| INTERVAL BEFORE RELAPSE | PATIENTS ON CORTISONE | PATIENTS ON ACTH |
|---|---|---|
| *days* | | |
| 1–10 | 11 | 11 |
| 11–20 | 3 | 0 |
| 21–31 | 2 | 0 |
| 31–60 | 2 | 1 |
| 61–90 | 0 | 0 |
| 91–120 | 0 | 0 |
| 121–150 | 0 | 1 |
| Undetermined | 4 | 4 |

The rapidity of return of symptoms upon cessation of therapy is shown in Table 1. No prolonged, significant remissions after hormone therapy were observed. Slight degrees of functional improvement occasionally persisted when subjective and objective findings indicated a relapse. Such improvement was attributed to increased joint motion, co-ordination

*This system divided the patients into four functional classes: Class I, ability to carry on all usual duties without handicaps; Class II, adequate for normal activities despite handicap of discomfort or limited motion in one or more joints; Class III, limited only to few or no duties of usual occupation or self-care; and Class IV, incapacitated, largely or wholly with little or no self-care.

and muscle strength achieved by the other measures instituted before or during hormone therapy. The time of relapse could not be determined in 8 cases in which improvement on therapy had been minimal and return of symptoms and signs insidious. Eleven patients relapsed within ten days of cessation of cortisone, and 11 within ten days of ACTH therapy. Complete relapses had occurred within sixty days of cessation of therapy in all but 1 case. This patient had received intravenously 20 mg. of ACTH daily for twenty-eight days and did not return to her pretreatment level until approximately one hundred and fifty days after therapy. It should be noted that precise measurement of the rate of relapse is difficult, and figures in this report refer to the time between cessation of therapy and return to the pretreatment baseline.

### Laboratory Results

Changes in the erythrocyte sedimentation rate are presented in Table 2. The rate usually decreased, but not always to normal (0.40 mm. per minute). It became normal in 12 patients receiving cortisone and 6 patients receiving ACTH but remained normal during therapy in only 5 in each group. It was unchanged in 11 patients receiving cortisone, but all patients receiving ACTH had some decrease. The sedimentation rate was normal before therapy in 1 patient receiving cortisone and in 2 receiving ACTH. Subjective, objective and functional improvement occurred in the absence of a significant fall in the sedimentation rate.

Table 2. *Changes in Erythrocyte Sedimentation Rate (Rourke-Ernstene Method).*

| Sedimentation Rate | Patients on Cortisone | Patients on ACTH |
|---|---|---|
| Decrease to normal | 12 | 7 |
| Maintained at normal level | 5 | 5 |
| Decrease | 18 | 8 |
| Unchanged | 11 | 0 |
| Normal before therapy | 1 | 2 |
| Undetermined | 0 | 1 |
| Totals | 42 | 18 |

Table 3. *Changes in Synovial Fluid.*

| Change | No. of Cases |
|---|---|
| Amount | ▼ 9 of 13 |
| Leukocytes | ▼ 7 of 13 |
| Polymorphonuclear leukocytes | ▼ 10 of 13 |
| Viscosity | ▲ 8 of 9 |
| Sugar | ▼ 3 of 8 |

The results of synovial-fluid examinations are shown in Table 3. The most constant alteration was an increase in viscosity. A decrease in the amount of fluid and the total number of leukocytes and polymorphonuclear leukocytes occurred in most cases. A marked increase in relative viscosity (from 13.4 to 6080.0 at 38°C.), which occurred in 1 patient during ACTH therapy, has previously been reported.[11]

### Histologic Results

Microscopical examination of tissue revealed essentially the same changes for both types of treatment. This response consisted principally of a decrease in edema and inflammatory cellular infiltration and some reduction in fixed cellular hypertrophy and hyperplasia. These changes were particularly well demonstrated in a patient who had had synovial biopsies of one knee before and after a hundred and ten days of treatment with ACTH. This case has previously been reported.[11]

In synovial specimens from another case on ACTH and 8 cases on cortisone, exudation and proliferation were relatively mild, but even after two hundred and thirty-five days on cortisone in a dosage that was never less than 125 mg. a day, and in the presence of manifest hypercorticism, inflammatory changes had not completely disappeared. Moreover, some focal necrobiosis persisted in the joint lesions and in the subcutaneous nodules. Seven of the synovial specimens showed foci of superficial fibrin-like material usually associated with some atrophy or loss of adjacent cells. In subcutaneous nodules removed from 2 patients both before therapy and after twenty-two days on cortisone and thirty-two days on ACTH respectively, there were typical large geographic regions of necrosis with no evidence of healing. In the cortisone-treated cases, however, in which marked reduction in the size of the nodules had been noted clinically, perivascular inflammation was reduced over that in the pretreatment biopsy, and the cells adjoining the necrotic regions were less hyperchromatic. In some regions these cells also seemed to have an increased amount of foamy cytoplasm as described by Fienberg and Colpoys.[12]

### X-ray Studies

Repeat x-ray examinations of involved joints were performed on 5 patients, after one year or more of continuous therapy with cortisone. Four patients had no changes indicative of either progressive destruction or repair of prior damage. One patient, who had chiefly hand and wrist involvement, manifested increased demineralization, adjacent to the wrists and small joints of the hands, narrowing of several proximal phalangeal joints and a cystic zone within the right carponavicular bone. These changes were considered indicative of progression of rheumatoid arthritis in spite of the fact that the patient had never received less than 100 mg. a day and had facial characteristics of hypercorticism.

### Side Effects

Complications of hormone therapy encountered in this study are summarized in Table 4. It was

necessary to discontinue cortisone in 8 patients and ACTH in 6 because of psychoses, marked fluid retention, thrombophlebitis, aggravation of diabetes or complicating infections. These morbid features of hypercorticism, which have all been previously encountered, are reviewed by Hench.[7] Facial changes, including moon facies, hirsutism and acne, were relatively frequent but, except for their psychologic effects, did not present a problem; in fact, they served as a constant reminder that a state of hypercorticism existed. Edema, presumably from a salt retention, usually was without ill effect in this series. A more serious complication in some patients was potassium loss, manifested by weakness and electrocardiographic abnormalities. In 1 patient, without previous evidence of heart disease, cardiac failure developed on cortisone, with peripheral and pulmonary edema and electrocardiographic evidence of potassium depletion.

TABLE 4. *Side Effects.*

| COMPLICATION | PATIENTS ON CORTISONE* | PATIENTS ON ACTH† | TOTALS |
|---|---|---|---|
| Edema (overt) | 7 | 5 | 12 |
| Hypertension | 6 | 5 | 11 |
| Low potassium syndrome | 2 | 3 | 5 |
| Electrocardiographic abnormalities | 10 | 2 | 12 |
| Cardiac failure | 1 | 0 | 1 |
| Moon facies | 17 | 9 | 26 |
| Hirsutism | 5 | 4 | 9 |
| Acne | 2 | 9 | 11 |
| Diabetes | 2 | 2 | 4 |
| Menstrual changes | 1 | 1 | 2 |
| Euphoria | 30 | 15 | 45 |
| Depression | 10 | 7 | 17 |
| Psychosis | 2 | 3 | 5 |
| Defective wound healing | 3 | 0 | 3 |
| Hemorrhagic phenomena | 1 | 3 | 4 |
| Thrombophlebitis | 2 | 0 | 2 |
| Infection | 6 | 5 | 11 |
| Pathologic fracture | 1 | 0 | 1 |
| Death | 1 | 0 | 1 |

*Total of 42 patients.
†Total of 18 patients.

Hypertension was rarely a problem since the increases in blood pressure were, as a rule, slight. Two patients receiving cortisone and 1 receiving ACTH had significant but transient elevations of the fasting blood sugar. One patient receiving cortisone had an aggravation of previously existing diabetes, which necessitated the discontinuance of therapy. Changes in mental status, which ranged from euphoria and minor depression to severe psychoses, have previously been described in detail.[18] Therapy was discontinued in all patients in whom psychoses developed and in 1 who became depressed.

Defective wound healing was observed in 3 of 13 patients who underwent operations while receiving cortisone, but in none of the 5 patients who were operated on while receiving ACTH. Delayed wound healing in 2 patients was associated with infection. The only hemorrhagic phenomena observed were petechiae and ecchymoses. Thrombophlebitis appeared in 2 patients receiving cortisone, and treatment was discontinued in 1 for this reason.

Infection developed in 6 patients receiving cortisone and 5 receiving ACTH. One patient receiving cortisone had a fulminating lobar pneumonia and died within twelve hours of the onset of symptoms.

In 2 postmenopausal women given cortisone compression fractures of the lumbar spine occurred. Both had roentgenographic evidence of osteoporosis of the spine at the time the fracture was discovered and had complained of severe backache that was distinctly different from previous back symptoms.

## DISCUSSION

The design of a therapeutic program using cortisone or ACTH involves many variables, including the hormone itself, route of administration, dosage, duration of treatment and concurrent therapeutic measures. Cortisone has been the more desirable preparation because of its effectiveness by oral administration and its relatively constant potency. The more purified preparations of ACTH, however, have been found to maintain more constant effects. Cortisone has been approximately as effective by mouth as by injection, although studies in 1 patient indicated it to be slightly more potent when administered intramuscularly. The route of administration of ACTH has been an important factor in determining its effectiveness. The initial preparations in gelatin were ineffective by subcutaneous injection and relatively impotent by intramuscular injection, whereas the more purified preparations have been effective by both routes of administration. Intravenous administration of the hormone assures adequate adrenocortical stimulation in small dosage and has been used in certain cases in which the potency of ACTH by the intramuscular route was questionable.

The dosage of cortisone varied during this study, initial high doses being used only in the early period. Lower starting doses, ranging between 100 and 150 mg. a day, were more satisfactory in that initial improvement more nearly approximated that obtained on maintenance therapy. Very low initial doses, followed by increasing amounts until improvement resulted, were unsatisfactory in that therapeutic objectives were unnecessarily delayed. Maintenance doses of cortisone varied in relation to therapeutic objectives and side effects. In these studies a maintenance dose was considered to be the amount of hormone that, in addition to conservative measures, produced subjective and functional improvement of a degree permitting a substantial increase in both comfort and functional capacity. Although a minimum of 75 mg. a day was required for complete vocational rehabilitation, subjective and functional improvement was noted in several patients on lower dosage.

The most satisfactory treatment schedule with cortisone began with 100 to 150 mg. a day, with a prompt decrease to 100 mg. daily as the rate of improvement diminished. After the initial reduc-

tion aspirin was resumed in full doses. When symptoms became stabilized on 100 mg. a day in addition to aspirin, cortisone was again reduced by 12.5 mg. every two or three weeks to the lowest level at which substantial improvement could be maintained. The results were more satisfactory when two or more weeks elapsed between changes in dosage.

Similar principles applied to the use of ACTH in determining initial and maintenance doses. Initial doses of 60 to 80 mg. a day were satisfactory when preparations of established potency were administered.

The interval factor in the administration of either agent varied with the agent used and the route of administration. Cortisone by mouth was effective when given every twelve hours, with a slightly larger morning dose. With the earlier, long-acting preparations of ACTH, one injection a day was inadequate, whereas a single daily dose of the more purified preparations was effective.

In this series of cases, hormone therapy represented but one component of a total therapeutic program. The conservative measures concurrently employed have previously been mentioned. It is believed that a good conservative regimen not only enhances the over-all therapeutic result from hormonal treatment but also helps to reduce the inordinate degree of dependence upon hormonal therapy that may arise in certain patients all too frequently to the point of neglect of good conservative measures. If these measures are emphasized as a critical part of the total management of the patient's illness, a good deal of disappointment may be precluded in the event that hormonal therapy proves ineffective or must be discontinued.

Therapeutic results have depended to a large degree on the type of patient treated. Patients in this series have fallen into three general categories: those with relatively inactive disease whose major problem was irreversible joint deformity — these gained very little from treatment except a slight increase in comfort; those with varying degrees of inflammatory activity whose symptoms and disabilities were more related to environmental and emotional factors than the disease itself and in whom substantial secondary gains from the disease had accrued — these seemed to respond to hormones poorly and occasionally resented them; and patients with obvious active rheumatoid arthritis with close correlation between the degree of inflammatory activity and degree of discomfort and disability — this group seemed to gain the most benefit from hormone therapy.

Certain patients in this series were selected because they presented special problems whose management might be facilitated by the use of hormones. This approach — to expedite the correction of joint deformities by the use of casts and traction — was disappointing even though the hormone was continued. Furthermore, its value in this regard was difficult to determine, since patients given hormone therapy without charge were anxious to co-operate and worked harder at their assigned tasks. As stated previously, some benefit accrued from special exercise procedures, particularly progressive-resistance exercises. Increased comfort made exercises more acceptable, and it is possible that, because of either increased co-ordination or muscle strength, a better functional status was attained. So little is known about the relation of these factors to motivation that no definite conclusions can be made.

Subjective improvement exceeded objective improvement during hormone therapy; the most constant response was a diminution of stiffness, soreness, pain, aching, weakness and fatigue. Hormonal therapy also induced various combinations of agility, "pep," endurance, optimism and euphoria, resulting in functional gains ranging from slight improvement in self-care to complete vocational rehabilitation.

The effective use of ACTH and cortisone was limited by the hazards of hypercorticism. The complications observed in this study have been well described in the literature and were recently reviewed by Hench.[7] Treatment was interrupted in 20 per cent of the patients receiving cortisone and 33 per cent of those on ACTH. During the earlier period of availability of the hormones, higher dosage was used, and complications were more frequent. The recent practice of limiting therapeutic goals and dosage has reduced both the incidence and the magnitude of these problems but has not eliminated them. No precautionary measure has been found that will obviate the necessity for constant observation of the patient. These and other studies have revealed that observations should be made of sleeping habits, unusual subjective sensations, personality changes, unusual skeletal and gastrointestinal symptoms, temperature, weight, skin changes, pulse, blood pressure, cardiac size and evidences of edema. Laboratory tests should include repeated urinalyses, and serum electrolyte determinations if alkalosis or low potassium syndrome is suspected. Preventive measures should consist of the selection of patients without relative or absolute contraindications to either hormone, the restriction of dosage levels to a minimum (initial doses of less than 150 mg. of cortisone a day and maintenance doses of 100 mg. or less a day), maintenance of adequate intake of protein, calcium and potassium, restriction of sodium intake and the discontinuation of therapy or the reduction of dosage when side effects appear.

Although cortisone and ACTH have an ameliorating effect on rheumatoid arthritis, it is apparent from the persistence of clinical evidence of synovitis, and progression as determined by x-ray examination, that neither agent completely suppresses the disease. In this study, complete objective remissions were

not observed. Moreover, examination of synovial tissue, after long-term therapy with doses sufficient to cause hypercorticism, revealed persistent evidence of synovitis, which included inflammatory cells and necrobiosis without evidence of healing. It can therefore be concluded that these agents are only repressive, and their use in this disease can be evaluated only in terms of the degree of improvement that can be obtained without serious complications of hypercorticism.

Because of the rapidity with which relapse occurs upon cessation of the drug, we are skeptical of the advantages of short-term therapy. It is true that slight improvement in muscle strength and coordination may be achieved from exercise programs during short-term treatment. However, it is quite possible that these gains could be accomplished without the hormone if the same degree of enthusiasm and encouragement were at hand. Although escape can occur with equal rapidity after long-term therapy, partial suppression of the disease during such treatment may make possible substantial gains in terms of comfort, activity and even rehabilitation.

## Summary and Conclusions

Cortisone and ACTH can favorably alter the clinical and laboratory manifestations of rheumatoid arthritis. The most immediate and impressive response is a decrease in symptoms, particularly pain and stiffness, and in consequence an improved functional status. Objective improvement is generally less than subjective improvement and is never complete.

Some histologic evidence of joint inflammation persists even after long-term therapy in doses sufficient to produce hypercorticism. Progression of the disease can occur under adequate hormone therapy as evidenced by x-ray examination. All patients do not respond favorably to these agents, their efficacy depending to a large degree on the type of patient selected for treatment.

The percentage of patients who can benefit from the hormones cannot be estimated from these studies. Hormone therapy should not be employed until maximum benefit from conservative measures has been established, and should always be combined with such measures. The total improvement that accrues is frequently a direct result of rehabilitation procedures facilitated by cortisone or ACTH or both. There is as yet no evidence that either agent alters the remission rate or the natural course of rheumatoid arthritis.

The hazards of hormone therapy include not only those directly associated with hypercorticism but also psychologic reactions that lead to a failure to adhere to conservative measures of proved value in the treatment of arthritis.

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# MODERN CONCEPTS IN THE TREATMENT OF OTITIS MEDIA*

BERNARD ZONDERMAN, M.D.†

BOSTON

THE purpose of this paper is to discuss several important aspects of the therapy of otitis media — namely, the use and abuse of antibiotics, the importance of myringotomy, the significance of serous otitis media and the problem of recurrences.

## CHEMOTHERAPY

The advent of chemotherapeutic and antibiotic drugs during the past fifteen years has dramatically changed concepts of the treatment of many diseases caused by bacteria. However, the development of resistance by certain bacteria, the emergence of superinfection by secondary pathogens and the increasing occurrence of undesired side effects have indicated that these drugs are not an unmixed blessing. Failures in the initial therapy of otitis media are increasing, and cases of mastoiditis with its several complications are more frequent than they were a few years ago. Deafness, especially in children, is more prevalent.

Romansky and Kelser[1] recently emphasized the fact that the antibiotics do not lessen the need for definitive diagnosis: "If anything, it is even more important to establish the precise indications for these agents and to diminish their indiscriminate use."

There is no doubt that the correct use of the proper antibiotics during severe bacterial infections of the upper respiratory tract has dramatically reduced the incidence of suppurative otitis media and its complications. But these dramatic results have led many physicians to an unwarranted complacency in the treatment of otitis media and a disregard for the important procedures of thorough history taking, meticulous examination of the nose and ears, careful testing of the patient's hearing and consideration of the sound surgical principle of myringotomy.

Rutherford[2] has summarized the problem as follows:

> Even in large teaching centers, interns and residents are not being taught the anatomy and physiology of the middle ear or a knowledge of the pathologic processes which may occur within it ... [This] has led to a state where the younger physicians do not know the art of cleansing the ear canals, of observing and recognizing the changes in the tympanic membranes ... or how to do a myringotomy. In fact, some of these young men and women have been taught that myringotomy is not only an unnecessary procedure but one to be avoided because it injures and scars the tympanic membrane, although spontaneous rupture of the drum under antibiotic therapy is not considered harmful. They do not differentiate between suppurative and nonsuppurative acute otitis media; the treatment is always one of the antibiotic drugs without regard to the bacteriology or pathology involved. If one drug does not bring results, another antibiotic is resorted to, or possibly "combined therapy," the shotgun method, is used.

## MYRINGOTOMY

Perhaps the most common error in the therapy of otitis media is undertreatment with antibiotics without myringotomy. This may lead to a temporary suppression of the bacterial infection, with subsidence of the acute symptoms of otalgia and fever, followed shortly by a more severe and hazardous recurrence. The following case illustrates this point:

> A 9-year-old boy was examined on April 27, 1953. Three weeks previously, after a head cold, otitis media had developed, with spontaneous perforation of the right eardrum. He was given an injection of penicillin and some penicillin and sulfonamide tablets for 24 hours. The symptoms of pain and fever rapidly subsided. He was given no further therapy. His hearing was not checked nor was the drum re-examined. The child told no one that his ear felt blocked and "funny." On April 24, 3 days before I saw him and 2½ weeks after onset, the mother noted some ear discharge, and 2 days later the child complained of pain and had a slight fever.
>
> Examination revealed a thickened, beefy eardrum, with a pouting nipple perforation, and a thick, purulent discharge from the middle ear. There was marked hearing loss on that side. A culture was taken. The nipple perforation was enlarged and a large quantity of pus suctioned from the middle ear. The patient was given oxytetracycline by mouth, 250 mg. 4 times a day for 6 days, with rapid subsidence of the infection, closure of the perforation, resolution of the drum and return of normal hearing. The culture produced a pure growth of beta-hemolytic streptococcus, an organism that has not shown resistance to penicillin.

If this child had had proper primary treatment — that is, an adequate daily dose of the antibiotic for a long enough time (at least five to seven days) — the recurrence could have been avoided, especially with early performance of myringotomy.

Undertreatment may also lead to superinfection, often by organisms that were once considered nonpathogenic in the days before antibiotic therapy, as illustrated by the following case:

> A 69-year-old man was seen on April 7, 1953. One month previously, after a mild upper respiratory infection, he had severe pain in the right ear all night, followed by a spontaneous perforation and a sanguineous discharge early in the morning and a persistent, painful throbbing in the ear. His physician gave him an injection of penicillin and prescribed some tablets, which he took for 1 day and then discarded because of improvement. Throbbing in the ear and discharge recurred several days later, and again he was given an injection of penicillin, with temporary improvement but with recurrence of symptoms a few days later. Two weeks after onset he consulted another physician. By now he had a profuse mucopurulent discharge, dull pain in the region of the ear and marked unilateral hearing loss. He was given chlortetracycline capsules. He took 6 of these, but, because of constipation, he discontinued taking them. His symptoms persisted, and he returned to the 2d physician who referred him to me.
>
> Examination revealed a profuse, mucopurulent discharge from a pin-point perforation in a thickened, inflamed drum.

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 21, 1953.

†Instructor in otolaryngology, Boston University School of Medicine; assistant surgeon, Winthrop Foundation, and Clinic for the Deaf, Massachusetts Eye and Ear Infirmary; associate visiting surgeon, Massachusetts Memorial Hospitals; associate in otolaryngology, Beth Israel Hospital.

The classic signs of mastoiditis — postaural tenderness and swelling and sagging of the posterosuperior canal wall — were absent. X-ray films revealed destruction of the mastoid cells in the region of the mastoid antrum and increased density.

The patient was admitted to the Massachusetts Eye and Ear Infirmary, where an extensive complete simple mastoidectomy and a wide paracentesis of the eardrum were performed 2 days later. The large pneumatized mastoid bone was found to be exclusively involved, with all mastoid cells filled with "chicken-fat" granulations and tenacious mucopurulent discharge. Cultures from the external ear canal, the middle ear and the mastoid cavity all grew out *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*), which was insensitive to penicillin and most of the broad-spectrum antibiotics. A catheter was sutured into the mastoid cavity, and the mastoid and middle ear were irrigated with 2 cc. of a solution containing 50 mg. of polymyxin per cubic centimeter twice a day for 4 days. The discharge rapidly subsided, the eardrum and postaural wound healed within 1 week, and the patient was discharged on the 9th postoperative day. The hearing has since returned to normal.

This case demonstrates the failure of inadequate antibiotic therapy to prevent mastoiditis and the development of a superinfection by a gram-negative bacillus that was rarely a cause of otitis media in the past and is now found with increasing frequency. It also demonstrates how the classic signs of mastoiditis may be masked by antibiotic suppression, indicating the need of a greater alertness by the physician and a carefully conducted follow-up study of the patient.

Another complication that is often lost sight of in enthusiasm for routine antibiotic treatment of otitis media without myringotomy is that of chronicity. The patient may pass through the acute stage of the disease only to be left with a chronically discharging ear with all its physical, social and economic problems. The dictum that "the cause of chronic otitis media is neglect" is more true today than it was fifteen years ago, since chronicity should be more easily preventable now than formerly:

> The practice, widely accepted among pediatricians and general practitioners, of allowing the eardrum to rupture when and where it will shows an appalling ignorance of the dangers of the chronically discharging ear. The site of the perforation has a bearing upon the prognosis, and while many drums rupture where healing is likely to occur, others may perforate in Shrapnel's membrane leading to a chronic suppuration in the attic with all its dangers of extension of the disease to the labyrinth, lateral sinus, facial nerve, and meninges.[3]

The results of treatment of chronic otitis media by antibiotics alone are disappointing. More and more, organisms insensitive to most or all of the antibiotic drugs are being cultured. Sixty-five per cent of staphylococci, for example, are insensitive to penicillin, and 50 per cent to chlortetracycline. The best treatment is still prevention of chronicity by adequate therapy during the acute stage.

It is the consensus of leading otologists that the most effective measure in the prevention of otitic complications and chronicity is a properly performed myringotomy early in acute suppurative otitis media coupled with adequate dosage of the proper antibiotic agent (as determined by culture after myringotomy) for a long enough period (at least five to seven days) and a carefully made follow-up study of the patient until the discharge has ceased, the perforation has healed, the drum has resolved, and the hearing has returned to normal.

## Serous Otitis Media

One type of middle-ear disease that has been noted with increasing frequency in recent years by otologists but is not sufficiently appreciated by the medical profession at large is that of serous otitis media (also known as "secretory otitis media," "otitis media with effusion," "mucus otitis media" and hydrotympanum). This condition most frequently follows an acute upper respiratory infection, with resultant swelling and obstruction of the eustachian tube and accumulation of a sterile (nonpurulent) fluid in the middle ear. Often, the condition represents an aborted suppurative otitis media that has been sterilized by antibiotics, leaving a nonpurulent straw-colored fluid of high-protein content in the middle ear. If this fluid is not evacuated, it leads to adhesive changes in the middle ear and causes a permanent conduction deafness. Undoubtedly, serous otitis media contributes to the alarming increase in hearing loss in children reported in recent school surveys. Other causes of secretory otitis media include hypertrophied lymphoid tissue in the nasopharynx in children, the increase in air travel and aerootitis media, nasal and ear allergy and virus infections. In adults, serous otitis media may be the first clinical indication of an underlying neoplasm of the nasopharynx.

In describing their symptoms, adults often complain of a "numb," "stopped-up," "blocked," or "full" feeling in the ear or head. Some state quite accurately that they have water in the ear and at times can feel fluid "crackling" or "bubbling" upon blowing the nose or sniffing. A diagnostic symptom, if the middle ear is only partially filled, is the temporary improvement in hearing when the patient tilts the head toward the affected side or lies down. In young children the only symptom is usually an impairment of hearing that has been noticed by the parents or the schoolteacher or after routine school audiograms.

The diagnosis should be suspected from the history. Otoscopic examination often reveals the drum to be a shade of yellow, somewhat more translucent than normal, occasionally having a shiny wrinkled appearance, with a chalky-white color of the malleus. Rarely, a fluid line is seen that shifts position with tilting of the head. If the middle ear has been inflated, definite air bubbles may be seen through the drum.

Treatment varies from nasal vasoconstriction and inflation of the middle ear by politzerization to catheterization of the eustachian tube, aspiration of the middle-ear contents and myringotomy,

repeated as often as necessary to evacuate the fluid and re-establish normal hearing. Myringotomy of the noninflamed drum is not a painful procedure and can often be performed with ease and without anesthesia, even in young children.

## Recurrence

Recurrences of otitis media — of both the suppurative and nonsuppurative variety — often present a problem in therapy. Needless to say, the underlying or predisposing causes must be diligently sought by careful examination of the nose, sinuses and nasopharynx, and treated. In children, a well performed adenoidectomy (or secondary adenoidectomy) often gives excellent results. In recent years the usual technic of adenoidectomy, performed blindly, without direct visualization of the nasopharynx, has been abandoned. Inspection of the nasopharynx after adenoidectomy by the blind technic — even when expertly performed — usually reveals large masses of adenoid tissue remaining about the orifices of the eustachian tubes and in the fossa of Rosenmüller. In children with a history of recurring otitis media or hearing loss with head colds, the method of direct, complete adenoidectomy, performed with the patient in the sitting position, the soft palate elevated with the Lothrop or the Love soft-palate retractor and the nasopharynx exposed to direct inspection, is preferred. The main adenoid mass is removed in the usual manner with the adenotome. This is followed by meticulous and methodical removal of the remaining islands or lymphoid tissue under direct vision by specially devised adenoid punches provided with a basket attachment. This direct adenoidectomy technic permits a much more thorough removal of the offending lymphoid tissue masses about the eustachian-tube orifices and gives better results in attempts at prevention of recurrences of otitis media and hearing loss. Incidentally, this technic also diminishes the frequency of postoperative adenoid bleeding.

In certain selected cases in which careful inspection of the nasopharynx reveals no gross islands of lymphoid tissue but in which there is recurring edema and inflammation of the eustachian-tube orifice, with resultant obstruction to ventilation of the middle ear (and consequent hearing loss), radiation therapy with the nasopharyngeal radium applicator or with x-rays may be beneficial in preventing recurrences or further hearing loss. Time does not permit further discussion of this important and controversial subject. Such therapy should be performed only by specially trained and competent personnel under carefully controlled conditions.

Lastly, I mention the promiscuous use of antibiotic troches and lozenges in the prophylaxis or treatment of recurrences of pharyngitis and otitis media only to condemn it as vehemently as I can. Not only are these antibiotic lozenges and troches therapeutically useless but also they have produced a host of complications varying from allergic side effects (including angioneurotic edema and severe stomatitis) to resistant organisms and superinfections with such organisms as *Haemophilus influenzae*, staphylococci, *Proteus vulgaris* and *Ps. aeruginosa* and frank moniliasis. Their use should be entirely abandoned.

## Summary and Conclusions

The physician treating otitis media has a dual responsibility to his patient. The first is the prevention of mastoiditis and chronicity, and their hazardous intracranial complications. With the aid of the sound surgical principle of myringotomy and the judicious and adequate use of antibiotics, one can undertake this responsibility with justifiable confidence in the great majority of cases.

The second responsibility in the treatment of otitis media is the conservation of hearing. Otitis media is not just a bacterial inflammation. It is a disease of the hearing apparatus. The products of inflammation — whether purulent or not — must be removed before permanent hearing loss ensues. The hearing must be carefully checked and rechecked. A deafened ear, even though bacteriologically cured, represents a therapeutic failure.

314 Commonwealth Avenue

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# AN APPROACH TO THE "SKID ROW" PROBLEM IN BOSTON

DAVID J. MYERSON, M.D.*

BOSTON

IN every city there are many men whose dominating drive and desire to drink have led them to an existence so submarginal that they represent a serious social, economic and health problem to all community-minded citizens. This paper discusses the characteristics of such alcoholic patients observed in the Long Island Hospital, Boston, Massachusetts, and describes the rehabilitation program now operating at this hospital.

These are homeless men. Whether high-born or low-born, intelligent or stupid, religious or agnostic, they have lost or abandoned all previous personal contacts, and drift alone through the rooming-house sections of Boston, such as the South End, Scollay Square and some parts of the West End. Some work at temporary jobs, as dishwashers, short-order cooks, porters or hospital attendants. Others beg, and not a few steal or forge checks. However they obtain money whether legally or illegally, its primary value to them is the alcohol it buys. Food, clothing, shelter, family responsibilities or debts are all of secondary importance. Indeed, everything in these people's lives is directed toward the consumption of alcohol in any form. Drinking habits vary: they may drink alone or with a group, continually or in vicious, prolonged sprees. Their ability to survive the ingestion of tremendous amounts of alcohol, so often mixed with the most dangerous toxins, is a source of continual surprise to the medical observer. Of course, physical scars, such as cirrhosis of the liver, peripheral neuritis and brain damage, are often present, and the Boston City Hospital repeatedly cares for men whose bodies have failed to withstand this continual stress of poison, poor nutrition and extremely low-grade living conditions. Nevertheless, hardy men do survive and live to an advanced age.

A study of the social background of these men reveals that most are native born and that most come from the lower to middle economic groups, and a few from socially prominent families. Almost all are either of Irish or British descent (actually 74 per cent Irish, 20 per cent British and 6 per cent others), with the former predominant. There are a few of Scandinavian or German descent, but these as a rule have drifted in from other parts of the country. So far, representatives of other minority groups, such as Italians, Jews and Negroes, have not appeared in this Long Island group.

Since most of these men are forty years of age or over, information regarding their family histories is sparse. By and large, the parents have died off and the men are reluctant to discuss them. The siblings, if any, often will not tolerate them and have given them up for lost. Frequently, a man's history indicates that he was not a community problem as long as his mother was alive, but with her death he lost his protector and had to subsist on the existing community facilities. If married, he has long since divorced or separated from his wife. Occasionally, a vindictive wife will get revenge for her years of misery by insisting that the husband go to jail for nonsupport. As a rule, the woman seems to adjust herself to life without her husband and insists only that he leave her alone. (In this group 40 per cent of the men are single, 4 per cent married, 14 per cent divorced, 38 per cent separated, and 4 per cent widowed.)

Only 12 per cent give a history of alcoholism in the family, but it must be emphasized that the family history is obtained by direct questioning and therefore is unreliable. Of their early training, almost all, whether Protestant or Catholic, state that they were brought up in homes where religion was stressed. Just as they have lost contact with their families, so they have turned away from religion, not because they have become nonbelievers but because they consider prayer or confession futile in view of the repetitious and endless pattern of their drinking.

It must be borne in mind by anyone who attempts to deal with these people that for years they have always surrendered to an overwhelming impulse to drink and that gratification of this impulse represents their foremost pleasure in life. Thus, whatever their motivation for giving up alcohol, whether through sickness, disgust or fear, the deeply imbedded desire to drink remains forever and has led to the axiom: "once an alcoholic, always one." Through painful experience, one has learned to disregard their protestations and to consider their self-confidence as false and their optimism as unrealistic.

It must also be recognized that, no matter how friendly or understanding one is, the alcoholic patients may regard the doctor as standing in the way of the attainment of their satisfaction. Thus, in this sense, the physicians are their enemies and must expect and accept their hostility, sometimes quietly and sometimes vociferously expressed. Indeed, to the alcoholic person, the whole world must seem his enemy, for no one can really understand how deep his desire is. The sacrifice he has made of all that is important in life and the depths of misery he has reached offer clues to the intensity of this desire.

*Instructor in psychiatry, Tufts College Medical School; assistant physician, Department of Psychiatry, Boston Dispensary; consultant in psychiatry, Long Island Hospital.

Whether the years of giving in to their desires have led to the alcoholic personality or whether this personality itself leads to alcoholism, no one knows for certain. Nevertheless, these men exhibit certain general characteristics that create problems in any therapeutic situation. Thus, the tendency to blame others, the bursts of hostility upon the slightest frustration and the extraordinary sensitivity to what others think make them appear almost paranoid at times. Another common characteristic is an insatiably demanding nature. People who try to deal with such a patient must be careful not to give in to any of his demands, for once this happens, the demands may well continue beyond reasonableness. When finally he has to be refused, he bursts into rage and projects the blame on those around him. They, in turn, lose patience and have nothing further to do with him. Although hostile reactions are inevitable, anger should not lead to punitive measures. It is a certainty that throughout the life of the alcoholic patient all forms of punishment, threats, desertion and incarceration have been tried, all without success.

Up to the present time, judges, police and probation officers, city physicians and welfare workers have had most experience in dealing with these difficult people. While realizing the futility of jail, city or state hospitalization, these workers have had no choice but to incarcerate them over and over again.

Every understanding and interested observer knew that the alcoholic person was caught in a vicious circle from which there seemed to be no way out. Whether jailed or hospitalized, he received adequate care, but when he left either institution, he was utterly destitute, with rags as clothes and with empty pockets. If incarcerated for any length of time, he developed a deep dependency on the institution. After departure, without any place to go, he felt bewildered, frightened and so alone that even crossing through heavy traffic in downtown Boston was a tremendous effort. If he found a job, he had to wait two weeks, as a rule, for his first pay check. During this time the only place where he could sleep was in a flop-house, where all too often he became lousy. The lousiness, the poverty and the complete desolation, as well as his own fears and discouragement, made it impossible to break into the cycle of his drinking. It is no wonder that he became resigned to his life as a destitute alcoholic.

Before the Long Island Hospital program, which has been in operation for over a year is discussed, a few remarks about the institution are pertinent. Despite the fact that the hospital has been in existence since 1894 and has a population of 1200 patients, its purposes and value have been unknown to many doctors.

Situated on one of the most attractive islands in Boston Harbor, the Long Island Hospital is set up to administer medical and surgical treatment to 800 chronically ill patients suffering from paraplegia, multiple sclerosis, arthritis, muscular dystrophy and cardiac disturbances. In addition, there are 400 dormitory patients, the vast majority of whom represent derelict alcoholics. Before 1950, the island was isolated, and a ferry was necessary for transportation to and from the mainland. With the completion of the bridge, there has been a burst of sustained energy, leading to considerable improvement in all directions of care and treatment.

The problem represented a tremendous challenge to the ingenuity of the hospital administration, social workers and psychiatrist responsible for their care. Some of these alcoholics had been there for years, adjusting themselves to the hospital and fearing to make any attempt to return to society. Others seemed to drift in and out, with a few achieving as many as 30 admissions in ten years. Still others lived a nomadic life: in the summer they earned their board and room at New England resorts. Intending to go to Florida in the winter, they went on a spree instead, were stranded in Boston, and were forced to spend the winter in the Long Island Hospital.

All these men were at first pessimistic and suspicious about any form of help. Indeed, they exuded a feeling of hopelessness that spread not only amongst themselves but also to the employees of the hospital. Nevertheless, it was believed that whatever the program, it would at least be an improvement over the prevailing situation. To be reasonably successful, a program for rehabilitation had to take into account several factors: a large number of utterly destitute men to deal with who had for years lived without self-control — to expect them to improve without some form of protection was unreasonable. The degree of protection, therefore, had to be neither too much, which would lend to dependency, nor too little, which would lead to drinking. Finally, it was necessary to avoid giving in to the dependent and demanding nature of these men.

After many months of trial and error, a rehabilitation program was adapted from the part-time protective environment and working parole system introduced by Dr. J. Thimann at the Washingtonian Hospital in Boston.* Allowing the patients to work outside but reside in the hospital for an extended period proved to be of considerable value. In the first place, this plan means that 40 to 50 men can be handled at one time. In the second place, the men are protected during their free time while learning to live without alcohol. As further protection against drinking, they are given "Antabuse" (disulfiram), a medicine that they know will make them ill if they drink. In

*Thimann, J. Part-time protective environment and working parole as adjuvant in treatment of alcoholics. *New Eng. J. Med.* 231:9-11, 1944.

the third place, the feeling of "handouts" is avoided as much as possible. These men are given nothing except the opportunity to work toward their own rehabilitation.

To describe the program in detail, a case history is presented:

Mr. B., a 42-year-old man, heard about the program while confined at Deer Island, the city jail, where he had been a number of times. His drinking had begun about 20 years previously, and for the past 10 years he had not been sober except when incarcerated in hospitals or jails. Ten years before, he had separated from his wife and his 2 children. The marriage had been characterized by quarrels, threats, pleadings, separations, false promises and unsuccessful reconciliations. Finally, after every effort to make him renounce alcohol had failed, his wife gave up the marriage. Since then he had adjusted himself to the "Skid Row" life, working a short time, living alone, drinking until exhausted, then being hospitalized or jailed; and repeating this pattern endlessly and hopelessly.

The patient came from a middle-class family. He described his mother as strict, but evidently with a tendency to favor him, the youngest child, in a family of 2 boys and 2 girls. His father drank somewhat, worked every day and did not take an active part in the family life. None of his siblings drank except socially. They were all married, and 1 brother had risen to prominence in his particular field.

The last time the patient left Deer Island, he applied for admission to the Long Island Hospital at the Registration Division of the Institutions Department at the Boston City Hall. All admissions are voluntary and remain so throughout the hospital stay. After several weeks' stay in the hospital, he applied through the Social Service Department for placement on the program. Commissioner John R. McGillivray first interviewed him to evaluate the patient in terms of his general social background and his motivating factors. After this interview, the patient underwent a thorough physical examination under the supervision of the clinical director of the hospital. Despite all the years of drinking, he was found to be physically well.

His reasons for joining the program were superficial indeed. Despite his history, he believed that there was not too much of a problem, but he had noted that some of his old drinking cronies, who were on the program, looked well and had good jobs. The Commissioner was skeptical about these motivations and therefore suggested a good deal of help before allowing him to go on the work program. Next, I interviewed the patient and followed him weekly, along with the social worker.

Progress was not easy. When the patient was told that the first part of the program consisted of work on the hospital grounds for 1 or 2 months, he threatened to leave. He made demands for special privileges, which were refused. When he was given the explanation that the program was designed to help him and was completely on a voluntary basis, he accepted it. He worked as close to an 8-hour day as possible. He helped in the hospital maintenance, and for several hours a day worked in the occupational-therapy department, where his work habits were noted. He was found to be an excellent worker, co-operative, but somewhat aloof. During his weekly interviews with the psychiatrist, he gradually became more at ease, so that he was able to discuss some of his personality difficulties and became more aware of the nature of his alcoholic problem. (Generally speaking, with these patients it is best to keep the therapy on a superficial level and develop a friendly relation.)

After his 3d week on the program the patient was placed on "Antabuse" (disulfiram), as all patients are unless it is physically contraindicated. Experience at this clinic has led to a dosage of 0.5 gm. daily for the first 2 weeks followed by 0.25 gm. for an indefinite period; many patients express a good deal of anxiety concerning this medication, so that much explanation and reassurance are necessary. This patient complained of drowsiness after being placed on the drug, but this did not last for more than 2 weeks. (The administration of the medication is a problem in itself, since patients often secretly and sometimes cleverly avoid swallowing the medicine; the attendant or nurse must be made aware of this difficulty, and it is suggested that the medication be ground up and swallowed in water.)

During the time in the hospital, attempts are made to mold the men into a group. They spend all their free time together. They live in a separate wing of the hospital. They eat together and participate in the hospital entertainment. To students of group dynamics, the observations are interesting indeed. Bizarre rumors flash in and out. The most insignificant complaint or the slightest favoritism or deprivation becomes magnified into the grossest injustice. Envy and rivalry can become so intense that there are always one or two patients who think that they are losing out, who leave the hospital in a rage, and end up on a terrible spree. Nevertheless, the majority of patients form a kind of *ésprit de corps* that is of value in overcoming their loneliness. To enhance this group solidarity and to encourage contact with understanding people outside the hospital, the patients are requested to attend meetings of Alcoholics Anonymous one evening a week. Many of them gain considerably more insight into the nature of their drinking through this group, and they certainly enjoy the friendliness of the meetings. Mr. B.'s aloofness was noted by all at first. Gradually he relaxed, and toward the end he became an active participant in the meetings.

After about 5 weeks on the program, he was allowed his first test on his own. Since he was completely destitute, he was permitted to go to the Morgan Memorial daily for 5 or 6 days to work for his clothes. After each day's work, he returned to the hospital, where he was checked by the Social Service Department. After this period he received a suit of clothes in payment for his work. (This part of the program is important, because in this way the patient avoids the feeling of being a charity case and, like any other member of society, what he works for has infinitely more value for him than what is given him.)

After the patient had earned his clothes at the Morgan Memorial, he was allowed to look for work, with the important stipulation that when he obtained a job, he continue to live at the hospital for not more than 6 months. With this goal in view, he was referred to the United States Employment Agency. He had had experience with machines and was referred for this kind of work when it became available. After 3 weeks of searching he found a job.

Once on the job, he commuted to work from the hospital every day for as long a period as he wished (usually up to about 6 months). During this time he paid for his board and room so that he would have a feeling of independence. On week ends he was given a pass. He went to see his wife, with whom he had had little contact for the past 3 years. After a polite conversation, she excused herself to go out with another man. The patient was seized with such an unreasonable fit of jealousy and depression that a nearly disastrous drinking bout occurred. The reaction to disulfiram prevented him from a prolonged bout. (This incident is characteristic of the demanding, unreasonable and sensitive nature of the alcoholic.)

By and large, most of the men make a surprisingly good adjustment while they are working and living in the hospital. This patient's whole appearance improved. After the episode with his wife, he became considerably more reasonable and more realistic about himself and his situation. He re-established contact with the few remaining members of his family. He returned to his church. Finally, after 5 months, he decided to leave the hospital to live in a rooming house near his sister, who was willing to have him visit and eat with her whenever he wished. With his departure contact with him ended, except for occasional letters and reports from other patients.

This case demonstrates the technic and the problems of the Long Island Hospital program. Between February 15, 1952, and March 2, 1953, 119 people have applied for this rehabilitation program. Of these, 8 were immediately disapproved, and 16 left after several weeks. The remaining 95 men completed the program in its first year of operation. Of these, 45 were single, 31 separated, 13 divorced, and 6 widowed. Twenty-eight patients were between thirty and thirty-nine years of age, 59 between forty and forty-nine, 7 between fifty and fifty-five, and 1 over fifty-five. Thirty-five men had completed grammar school, 34 had attended high school, and 26 had completed high school or college.

Of these 95 patients, 31 completed the program successfully and left the hospital fortified with

money, clothes and a job. Two of these had failed once while on the program; 3 had two relapses, and 2 had three relapses before successfully completing it. Of this group of 31, 16 re-established contact with their families. As of March 2, 1953, 16 men were employed but still living at the hospital. Most of the failures suddenly disappeared, never reporting back to the hospital either from the Morgan Memorial or from work. It is noteworthy that while on the hospital grounds, patients rarely drink.

## Discussion

It is difficult to present a valid interpretation of these figures because of the relatively short period involved and the nature of the problem. In evaluating the results of this program, one must realize that the problem is approached symptomatically and not curatively, since the cure for alcoholism is unknown. Should one, for example, evaluate the results by comparing the patient's present drinking habits with his past? Or should one set up an arbitrary goal — such as a two-year period of sobriety — to constitute success or failure? At present, it is perhaps best to omit answering these questions.

However, it is fair to conclude that the outstanding value of the program is that it offers a real opportunity for breaking the vicious circle of the alcoholic patient, who, destitute and frightened, leaves a hospital only to drink as soon as he can. Through this plan of partial protection, he is given the opportunity of learning to live without alcohol. What he does with this opportunity depends to a large extent on his inner resources, which certainly cannot be rated highly.

With such men, who have been incapacitated for so many years, although many failures are expected, it is discouraging, indeed, to see men who look so well leave the hospital and drift back to their previous dreary existence. This brings out the weakest point in the program — namely, the fact that there is no adequate follow-up study, since the hospital is located too far from the center of the city. It is planned, in the very near future, to establish an evening clinic in the heart of the city with the hope that continuation of the therapeutic relation may prolong the period of sobriety of these men.

Another goal of this project is the research program, which has recently been instituted. The need for further insight into the nature of these people is apparent. I know of no disease, if it can be considered as such, that involves in so complex a way cultural background, physiologic processes and emotional difficulties. One can therefore consider alcoholism a sociopsychosomatic disease. The setup at the Long Island Hospital offers a unique opportunity for studying each of these important approaches to the alcoholic problem.

As a sociopsychosomatic illness, alcoholism is also a community problem, and any intelligent and practical approach to it must keep this in mind. Thus, working personnel includes the commissioner of a city hospital, physicians, a psychiatrist, social workers, occupational therapists, nurses and attendants, Catholic and Protestant chaplains, a Methodist agency (the Morgan Memorial), the United States Employment Agency and Alcoholics Anonymous. Each one works together as on a team and is vital and indispensable in the rehabilitation of these seriously impaired patients. It is hoped that in the future judges, probation officers and the police, all of whom are involved in this problem, will be added to this collaborative team and make an important contribution, especially in referral and follow-up study of the patients.

## Summary

An attempt to deal with the problem of the derelict alcoholic in terms of a rehabilitation program is described. The background and some of the emotional difficulties of this group of patients are emphasized to point up the seriousness of the problem and the difficulty in dealing with it.

The technic of such a rehabilitation program, as it operates at the Long Island Hospital, is also described, with the primary goals of helping to attain sobriety for the patient and returning him to work in the community under the partial protection of the hospital.

The values and weaknesses of the program are discussed.

# MEDICAL PROGRESS

## ENZYMES IN CLINICAL MEDICINE

### Recent Developments in the Practical Application of Enzymes to Clinical Medicine

HENRY J. TAGNON, M.D.*

NEW YORK CITY

THIS paper is restricted to a discussion of recent developments in the field of practical applications of enzymes in clinical medicine. No attempt can be made to discuss the general significance of enzymes in medicine because such an undertaking would be equivalent to reviewing the whole field of biochemistry as applied to medicine. It is generally recognized that, with a few exceptions, every chemical reaction occurring in the cells of the organism is catalyzed by enzymes.[1] It follows that the study of normal metabolism at the fundamental level consists mostly of the study of chemical reactions that are made possible by the participation of enzymes. The study and recognition of deranged metabolism or, in other words, of disease — with the aim of correcting it and restoring normal health, which is the proper object of medicine — are therefore largely based on enzymology. Advances in understanding of the pathogenesis of disease are mostly expressed in terms of biochemistry, and this is also what constitutes the basis for rational therapy. Therefore, advances in medicine require more and more a basic understanding of enzyme action.[2] It is becoming apparent that the informed clinician should have an appreciation of the broad principles of enzyme reactions without which a modern knowledge of pathologic processes has become impossible.[3]

One may conjecture that enzymology occupies, in relation to present-day medicine, the position that pathology had a generation ago. No doubt a knowledge of pathologic morphology is still important, but enzymology now represents just as important a basis for the understanding and treatment of both acquired and hereditary diseases. Many of the latter are explained by the probable existence of a specific gene for every specific enzyme within the cell.[4] A mutation may lead to the loss of an enzyme, engendering a constitutional and hereditary disturbance.[5] The physician who treats diabetes requires an understanding of the normal metabolism of carbohydrates, which consists of a succession of enzyme reactions whose speed and direction are influenced by the presence or absence of various cofactors, changing concentrations of substrates, different hormones and so forth.[6, 7] Insulin is one of the many hormones that influence the speed and direction of these enzyme reactions.[8] One major metabolic block in carbohydrate metabolism in diabetes is the inability to form glucose phosphate from glucose.[9] The reaction is catalyzed by the enzyme hexokinase. This concept of the metabolic block in diabetes constitutes the basis for recent studies on the possible usefulness of fructose, because fructose is phosphorylated independently of glucose and there is no block of this reaction in diabetes.[10] This example shows the importance of a basic understanding of the enzymology of diabetes so that the physician will appreciate the principles of treatment and be able to adapt his therapy to the changing situation of the patient.

Enzymes are organic catalysts, and in the definition of Ostwald a catalyst is "an agent which affects the velocity of a chemical reaction without appearing in the final product of the reaction."[11] For instance, colloidal platinum, which is a simple catalyst, catalyzes the decomposition of hydrogen peroxide into water and oxygen. A catalyst does not create a chemical reaction. What it does is to affect the rate of the reaction that it catalyzes.[12] A second important characteristic is that the effect of the catalyst is normally out of all proportion to the amount used. For instance, a minute quantity of colloidal platinum is sufficient to catalyze the decomposition of an unlimited amount of hydrogen peroxide. This is also true in a certain measure for enzymes, which differ from other catalysts, however, in that each enzyme catalyzes one kind of reaction only.[12] Chemically speaking enzymes are protein and have a high molecular weight. It follows that they are generally inactivated by heat. They can usually be extracted from the cells in which they are produced.

A general discussion of enzymes and their properties is outside the scope of this review. Reference has been made to their role in the pathogenesis of disease. Of immediate interest to the physician is their introduction in clinical medicine as diagnostic and therapeutic tools. Some of the recent developments in this field are discussed.

#### USE OF ENZYMES IN THERAPY

A consideration of enzymes as therapeutic agents is logical if one remembers that enzymes are biologic catalysts of high specificity capable of promoting vitally important chemical reactions in the presence of adequate amounts of suitable substrate.

*Associate professor of clinical medicine, Cornell University Medical College; associate, Sloan-Kettering Institute; associate attending physician, Memorial Hospital; assistant attending physician, New York Hospital.

It is natural that one would hope to influence biochemical reactions in the organism by the administration of suitable enzymes. However, many conditions have to be fulfilled before an enzyme can be used therapeutically. Also, there are many theoretical difficulties that must be circumvented before useful results can be expected from the administration of enzymes.[13] In the first place, these substances are protein, and they have to be prepared from animal tissues.[14] The problem of antigenicity has therefore to be overcome if prolonged administration of these animal products is contemplated. For instance, it is well known that such enzymes as trypsin and pepsin are antigenic and that their antigenicity is species specific.[15] In this connection complete purification of the therapeutic enzyme is desirable because it eliminates the enzymatically inactive but antigenetically active bound proteins. It follows that only since purified and crystalline enzymes have become available as a result of the work of Sumner,[16] Northrop et al.[14] and Northrop[17] have practical attempts at using enzymes therapeutically become possible. Another difficulty originates from the nature and site of action of most enzymes. The majority are intracellular, and their site of action is in the cytoplasm of the cell. Therefore, therapeutic administration of the intracellular enzymes, to be efficacious, would have to result in the penetration of the enzyme into the cell. Many factors should make it difficult for parenterally administered enzyme to penetrate into the cells. For instance, it has been demonstrated that proteolytic enzymes like trypsin and chymotrypsin do not penetrate into living cells under the most favorable circumstances. This is probably due in part to the fact that the membrane of the living cell is impermeable to this high molecular type of compound.[18] However, digestion takes place rapidly if the cells are killed. It is therefore doubtful if the simple parenteral administration of enzyme could generally result in an increase in the intracellular concentrations of the administered enzyme. Their protein nature makes it probably compulsory for most enzymes to be administered parenterally because the digestive activity of the gastrointestinal secretions destroys orally administered enzymes quite effectively.[19]

Finally, even if the enzymes could cross the cellular membrane there is little probability that they would localize at the intracellular site where enzymatic activity could take place. For instance, it is known that certain important enzymes like those associated with cellular respiration, esterification of inorganic phosphate and the Krebs tricarboxylic acid cycle are found in the particulate component of the cytoplasm in contrast to the enzymes responsible for glycolysis, which are easily extractable in water solution.[20] Many intracellular enzymes are found in the mitochondria, especially those associated with electron transport and oxygen activation, which represent fundamentally important metabolic reactions on which a therapeutic action could conceivably become desirable.[21] Yet it seems improbable at present that simple parenteral administration of this type of enzymes would result in their reaching the precise intracellular location where they could exert their activity. If enzymes, whose activity is associated with structural localization into the cell, are ever going to be useful therapeutically they will probably have to be "directed" by some methods to the cellular site where they can function. The nature of such a method of "directing" enzyme is, of course, not yet even conceivable. However, no one would certainly venture to predict that it will always be unknown.

Another consideration of importance in connection with the therapeutic possibilities is that many enzymes require cofactors for their activity. The well known enzymatic transformation of estrogenic compounds into inactive material by liver tissue in vitro is easy to demonstrate if liver slices are used in the experiment. However, this metabolic function disappears almost entirely if a brei made from these liver slices is substituted for the slices in the metabolic experiment. The activity can be restored if a simple compound like diphosphonucleotide (DPN) or niacin is added to the brei. The reason for this is that the DPN and niacin probably represent necessary cofactors that are present in adequate concentrations in the intact cells of the slices but become diluted or otherwise rendered ineffective when a brei is prepared.[22] There are many examples of the essential participation of cofactors in enzymatic activity. These cofactors are called coenzymes when they are loosely and temporarily attached to the enzymes and prosthetic groups when they are firmly fixed to their protein partner. Most water-soluble vitamins represent cofactors of biochemical enzymatic reactions.[23] Cofactors in general represent nonprotein moieties of varying chemical complexities. From a therapeutic point of view an adequate concentration of cofactors would have to be achieved, at the site of action of a parenterally injected enzyme, if such an enzyme required cofactors for its activity. The achievement of this aim does not seem to be impossible in view of the relatively simple molecular structure of cofactors.

It is because of these difficulties that the therapeutic use of enzymes has not progressed as fast as their availability seemed to justify. However, in recent years certain enzymes have been employed by parenteral administration with some measure of success. These attempts have been confined for the most part to bringing about a therapeutic action not requiring the penetration of the enzyme into the intracellular compartment of the body, and the use of enzymes that do not need cofactors for their activity.

So far the enzymes corresponding to these two conditions that have been used therapeutically have

belonged to the group of peptidases.[24] These are enzymes mainly concerned with the degradation of the large molecules of protein to yield smaller fragments. Some members of this group have been subjected to clinical trial and have shown promise in certain specific clinical situations. Nonproteolytic enzymes have been used therapeutically in an attempt to influence the intracellular metabolism of the body. Cytochrome is an instance of such a use, but experimental evidence has confirmed the validity of the theoretical objections against such a procedure by showing that parenteral injections of cytochrome do not result in incorporation of the enzyme into the cells.[13, 26]

Certain peptidases or mixtures of peptidases and other enzymes have been used therapeutically by injection into closed cavities like the pleural space or into abscess cavities. They have also been injected into the extracellular compartment of the body to obtain a systemic effect, and have been used in the form of local application on wounds and ulcer for the purpose of removing dead tissue and débris.

*Streptokinase-Streptodornase*

Certain strains of streptococci elaborate a soluble material that has the property of activating the proteolytic enzyme of plasma from its inactive state (proplasmin) into the active proteolytic enzyme, plasmin.[26, 27] This soluble material, which is present in the culture broth, is called streptokinase. The enzyme, plasmin, is then able to digest the fibrin and certain other proteins and to transform fibrin into soluble digestion products.[28] Streptococci elaborate also another enzyme called desoxyribonuclease or, briefly, streptodornase.[29] The substrate of this enzyme is desoxyribonucleoprotein. Thick, purulent exudates in pleural, pericardial cavities, for instance, or in certain abscesses are made principally of a mixture of fibrin and desoxyribonucleoprotein as well as of blood cells and tissue degradation products.[30] The two enzymes, streptokinase and streptodornase, produced by these strains of streptococci have been used for the liquefaction of purulent and hemorrhagic exudates in closed cavities,[31] in amebic abscess,[32] in unresolved pneumonia[33] and so forth. The beneficial effects result from the fact that drainage of pus is an essential element for successful treatment and the presence of viscous or insoluble material in the pus makes adequate drainage impossible.[31] Considerable loss of viscosity occurs in pus treated with streptokinase-streptodornase because of the degradation of fibrin and desoxyribonucleoprotein into smaller and less viscous molecules. The technic of using these two enzymes appears, therefore, to have a definite place in the treatment of conditions in which the main obstacle to cure is the difficulty of drainage of the exudate because of its viscosity. Adequate antibiotic therapy and other therapeutic measures short of surgical drainage remain, of course, important factors of successful treatment. The indications for this type of treatment, as well as the technic, have recently been completely summarized.[31] Isolated reports on the use of streptokinase-streptodornase mixture have also appeared and are difficult to evaluate because of the obvious lack of a statistical type of demonstration of effectiveness.[32, 33]

Although it acts directly on desoxyribonucleoprotein, streptokinase is not a proteolytic enzyme by itself but is really an activator of the proenzyme, plasminogen, which is present in blood plasma and should be present in the exudates, if streptokinase is to induce proteolytic activity. In the experience of the proponents of the method it has been found in exudate in amounts comparable to those of serum or blood. Other conditions necessary for optimum action of the enzymes in exudate have been listed, and the reasons for some of the failures of treatment have been discussed.[31] The general toxicity of these two enzymes appears minimal when they are evaluated by clinical and routine laboratory examinations.[34] However, no detailed post-mortem studies in animals and men have been carried out, and there is always the possibility that such studies would reveal lesions of the type, for instance, observed after the parenteral use of trypsin.[35] Streptokinase is a poor activator of the plasminogen of animal blood and cannot very well be evaluated by experimentation in animals.

These enzymes are definitely antigenic, and antibodies usually develop after a period of about two weeks, persisting up to three months after cessation of parenteral administration. A late appearance of antibodies is not usually an obstacle to treatment unless this has to be prolonged beyond two or three weeks.[31] It will be interesting to see whether the presence of antibodies against antigenic material of streptococcal origin in patients exposed to streptococcal infection can give rise to the type of diseases usually considered to be dependent on an antigen-antibody reaction. Such diseases have not been described so far in patients who received treatment.

The streptokinase-streptodornase mixture has also been used in local application on wounds, burns, ulcers and so forth to remove necrotic tissues and to liquefy thick exudates.[36-39] In general, the purpose is to achieve a type of medical débridement, and such a method has been called "medical débridement." Other enzymes have been used with the same purpose. Evaluation of this type of treatment of superficial wounds and ulceration is not yet complete although some good results have been reported.[38, 40, 41] But it should be understood that the objective is strictly limited to cleaning and that other measures to combat infection and hasten healing, such as the use of antibiotics and the fulfilling of nutritional needs, keep all their former importance. On the other hand when

purulent secretions tend to collect and obstruct drainage they provide a focus for the growth of pathogenic bacteria, and the cleansing action of the enzyme may represent an essential factor in the healing. An obvious theoretical advantage of medical over surgical débridement is the fact that in principle enzymes do not attack normal cells and surgical débridement is not as selective.[42] Nevertheless, it has been noted that treatment with streptokinase-streptodornase produced in some cases a tendency for the area of necrosis of the wound to spread.[42] Unfavorable reactions to the treatment have been reported in irradiation ulceration of the anterior chest wall. The manifestations were an increase in area of the ulceration as well as severe pyrogenic reactions, and it has been said that the use of streptokinase-streptodornase should be withheld in this type of lesion.[43]

In the treatment of wounds an adequate and prolonged contact between the enzyme solution and surface to be treated has sometimes constituted a problem. For instance, in burns and sloughs that are covered by hard and dried-out surface, the underlying necrosed tissue is protected from the action of the enzyme. This difficulty has been overcome in some cases by cross-hatching of the slough to allow penetration of the enzyme or by the instillation of the solution through drains inserted deep in the wound.[40]

Other enzymes, mostly of the proteolytic type, have been used in the treatment of wounds. As pointed out in a recent editorial the exact evaluation and usefulness of these treatments are not yet completed.[38] Papain, pepsin and trypsin have been applied on wounds, with valuable results.[40]

Obviously, much time will be required to assign a proper place to the medical débridement by enzymes, either as the main form or in association with the more orthodox surgical type.

### Proteolytic Enzymes in Treatment of Thromboembolic Diseases

The physiologic significance of the presence of plasminogen, the precursor of plasmin in circulating blood, is probably that it becomes activated when there is a need for the removal of fibrin in the body. Certain authors have considered that under normal conditions, blood clots continuously in the vascular system at a slow rate and that small amounts of fibrin continuously formed are subsequently removed by digestion, presumably through plasmin.[44] An increased velocity in the deposition of intravascular fibrin or failure of plasmin to remove the deposited fibrin could conceivably be a factor in the production of thrombophlebitis. It is therefore logical to attempt to treat thrombophlebitis by the administration of proteolytic enzymes in the circulating blood. This could be done by the injection of streptokinase, an activator of plasminogen, which is present in large amounts in normal plasma. Or it could be done by the intravenous administration of proteolytic enzymes that do not require activation, like trypsin and chymotrypsin.[45, 46] On theoretical grounds the administration of streptokinase seems to be the most attractive since its action results in the activation of the enzyme that presumably removes fibrin under physiologic conditions. However, the intravenous injection of streptokinase in amounts sufficient to activate significant amounts of plasminogen in the vascular system is pyrogenic. Therefore, streptokinase cannot be used unless the pyrogenic activity of the preparations now available is eliminated.[47]

Other proteolytic enzymes have been injected intravenously. There are several reports on the pharmacologic properties of trypsin injected intravenously in animals.[45, 48-50] It was found that trypsin has two types of effect, when so injected, both of which are toxic. In the first place, trypsin in small amounts is a clotting agent on blood in vivo as well as in vitro. The clotting action requires the presence of prothrombin and is most apparent when small amounts of the enzyme are used; larger amounts cause digestion of the blood-clotting factor. However, these larger amounts have been repeatedly found to be toxic for the animal species tested.[45, 49] They produce a type of shock that is similar to anaphylactic shock although no heparin is released in the vascular system as the result of the shock.[48] It was also well known that the toxicity of a given amount of trypsin could be greatly reduced by the slow intravenous administration as compared with a single injection.[45] However, this type of administration frequently resulted in local thrombosis of the vein at the site of the injection. For these reasons, and despite extensive studies carried out in different laboratories, trypsin was never used for the treatment of thromboembolic diseases in human beings, although its clotting properties were employed for the treatment of hemophilia.[51] In the first intravenous injection of trypsin in human patients, it was found that moderate amounts of the enzyme brought about a transient shortening of the clotting time of hemophilic blood when administered at a slow rate. The dangerous thrombotic activity was well recognized and intravenous injection for any purpose was not recommended. It was believed that their prolonged clotting time afforded some protection to hemophiliac patients against the thrombotic activity of intravenous trypsin but that injections in other human patients should not be attempted.[52]

The possibility of intravenous use of trypsin has been reinvestigated by Innerfield, Schwartz and Angrist.[53] These authors definitely confirmed the well established fact that slow administration is less toxic than rapid administration. They also confirmed the well known fact[45] that intravenous injection of trypsin reduces the level of fibrinogen and prothrombin in the circulating blood. How-

ever, they failed to make the observation that small doses hasten blood coagulation in vivo as well as in vitro. This failure is probably responsible for the optimistic reports of these investigators since the thrombotic activity is an essential point in the evaluation of the therapeutic value of this enzyme in thromboembolic diseases. There seems to be no question from the independent agreement of many laboratories[45,48,54] that such a clotting activity is really present and failure to observe it is difficult to understand.

In evaluating the therapeutic properties of trypsin, one must also consider the fact that blood plasma contains a powerful trypsin inhibitor. The quantitative aspects of the inhibition of trypsin by the serum inhibitor have recently been reviewed.[55] It was found, for instance, that 0.0003 cc. of human serum contained enough inhibitor to inhibit completely 1 microgm. of crystallin trypsin. If these results are correct — and they are well within the range found by other investigators — the small amounts of trypsin injected intravenously for the treatment of thromboembolic diseases that are nontoxic are probably also ineffective because they are completely neutralized by the serum inhibitor. There is therefore little to be expected from such injections.

In view of the presence of the serum inhibitor and of the fact that trypsin is a clotting agent in small and a shock-producing agent in larger amounts it appears that this enzyme is particularly unsuitable for treatment of thromboembolic diseases since the forbidding toxicity associated with rapid injections of proteolytically effective doses can only be avoided by a slow type of administration, which causes local thrombosis at the site of injection.[56] Obviously, such results are highly undesirable in patients with thromboembolic diseases. Undoubtedly, more work will be done on the subject, but in the meantime an attitude of extreme caution should be observed in the intravenous use of trypsin in human beings.[57]

Because of the importance of the problem of thrombophlebitis in clinical medicine and the possibility that the enzymatic approach might have important therapeutic promises one should also mention the work done with another peptidase obtained from the pancreas, chymotrypsin.[46] This has been obtained in a degree of purity comparable to trypsin, and theoretically chymotrypsin seems to be a much preferable enzyme for intravenous use because it has no clotting activity on blood and is generally less toxic than trypsin for the same amount of proteolytic activity. In animals, intravenous injections produce fibrinogenolysis and prolong the clotting time considerably. Chymotrypsin has not been utilized for the treatment of thromboembolic diseases in human beings. The authors responsible for the observation in animals noted that although proteolytic activity was detectable in the blood of the injected animals, preformed clots experimentally induced in dogs by crushing of the femoral vein on a steel wire introduced into the lumen were not affected by systemic injections of the enzyme. Even local injection of this powerfully proteolytic material into the vein around the thrombus failed to have a discernible thrombolytic effect. Further attempts were therefore abandoned. It is possible that changes in experimental conditions will provide a way to utilize chymotrypsin to dissolve intravascular clots. But preliminary evidence indicates as far as chymotrypsin is concerned (and this may obtain for some or all other proteolytic enzymes) that there is a considerable difference in activity if one compares the effect of identical doses on the circulating soluble fibrinogen, which is easily digested, and on the preformed venous clot, which shows great resistance to the agent. This difference is probably explained by the difference in the extent of contact between enzyme and substrate under the two different conditions. The difficulty will have to be overcome if therapeutic results are to be expected from the use of proteolytic enzymes in thromboembolic diseases.

Here, again, as with all proteolytic enzymes, the tissue should be carefully examined post mortem to rule out the possibility of irreversible changes associated with the injection of such material. These irreversible changes do not always express themselves by clinical manifestations.

More recently, the enzyme plasmin itself prepared from human plasma or fractions of human plasma proteins has been tried in animal experiments and appears to be a promising material.[58] The results are preliminary and cannot be evaluated at present.

This work on the use of enzymes in the relatively simple situation of thromboembolic diseases, in which the substrate is easily reached by parenteral administration and the conditions for the action of the enzyme are relatively favorable as compared with that in complicated intracellular enzyme systems, is a good example of the many problems offered by the enzymatic approach to therapy.

## Measurement of Blood Enzymes for Diagnosis

The measurement of enzymes and enzyme inhibitors in body fluids has long been proposed as a method for the diagnosis of certain diseases.[59-61] In certain cases, such as that of the acid phosphatase of serum, the measurement of enzymatic activity has a well established diagnostic significance in cancer of the prostate.[62] More recently, measurement of cholinesterase in the serum has been used in the diagnosis of liver disease, and in this condition it may yield information of value.[63] In the acid phosphatase of serum, the presence of increased amounts of enzyme reflects the activity of the prostate gland. Prostatic tissue contains a large amount of acid phosphatase, and this is true also for the tissue of the prostatic carcinoma.[64] Recently

Fishman et al.[65] proposed a chemical separation of the acid phosphatase of normal serum into one part originating from the prostate and another originating from nonprostatic sources. This separation could lead to an increased diagnostic sensitivity of the acid phosphatase test in cancer of the prostate.[65] The acid phosphatase as found in the serum does not appear to have any particular function, and therefore its only significance, so far, is diagnostic when increased amounts are detected. The situation of another constituent of the prostatic tissue is somewhat different; this is a proteolytic enzyme with fibrinolytic activity.[66, 67] The prostatic fibrinolysin has recently been found to be present in the plasma of a small proportion of patients with metastatic carcinoma of the prostate. The substrate for the prostatic fibrinolysin is represented by fibrinogen, fibrin, prothrombin, accelerator globulin and probably other proteins of the plasma. The number of patients in whom the prostatic fibrinolysin is found in the circulating blood is too small to give this determination diagnostic value. However, refinements of methods may lead to its detection in a greater proportion of cases. It should be pointed out that, in contrast to acid phosphatase, the presence of the prostatic fibrinolysin in the blood has important consequences because this prostatic enzyme is able to digest and destroy several of the factors of the blood-coagulation mechanism.[67] Thus, in patients with elevated fibrinolytic levels a pronounced decrease in the levels of fibrinogen, prothrombin and accelerator globulin may lead to a severe hemorrhagic diathesis.[67] The level of prostatic fibrinolysin in those patients has been shown to be influenced by the administration of hormones, especially estrogenic and androgenic hormones.[68] Thus, the administration of testosterone to a patient with carcinoma of the prostate can be shown to promote fibrinolysis and induce a rapid fall in the level of plasma fibrinogen, prothrombin and accelerator globulin. Hemorrhages may appear. Conversely, the administration of estrogen brings about the disappearance of fibrinolysis in the blood of the patient, and the blood clotting factors return to a normal level. Fibrinolysis associated with cancer of the prostate is a specific phenomenon that is never found in association with any other type of cancer. Another clinical condition in which fibrinolysis is occasionally observed is that of anoxemia associated with shock or other types of anoxemia. The few cases of fibrinolysis found in patients with nonprostatic types of cancer are probably attributable to the state of shock in which these patients were at the time that fibrinolysis was observed,[69] as discussed above.

Patients with cancer except prostatic carcinoma, far from showing fibrinolysis, often demonstrate an increased amount of trypsin inhibitor in the plasma.[61, 70] This fact has been recognized for a long time, and many attempts to establish this increased trypsin inhibitor as a test for the presence of cancer have been reported. As for all cancer tests, the type of control subjects needed in a study is not represented by normal persons but by patients without cancer who suffer from chronic or acute diseases like tuberculosis and pneumonia. Failure to apply this principle of investigation has frequently led to unjustified claims that a test for cancer diagnosis was discovered. In a recent study the trypsin inhibition of serum from patients with cancer was compared with that of normal subjects, patients with tuberculosis and patients with bacterial pneumonia. Trypsin inhibition was found to be increased in the serum of 59 per cent of patients with cancer, but increases of 45 per cent and 68 per cent, respectively, were observed in patients with tuberculosis and bacterial pneumonia. Of interest is the fact that inhibition of plasmin was found in these three groups of patients.[61] It therefore appears that changes in trypsin inhibition represent a completely nonspecific phenomenon and that, in its present form, this determination is of no use in the diagnosis of cancer.

Serum inhibition of other proteolytic enzymes has been proposed as a method for the detection of the response of cancer to treatment. For instance, it has been reported that the serum inhibition for renin and chymotrypsin fluctuates with the results of treatment in patients with cancer. The ratio of the inhibition for these two enzymes, according to the same authors, represents an important factor in the evaluation of treatment.[71] The data on which these conclusions are based are still preliminary and will certainly require extension and confirmation. It is possible that continued study in this direction will establish the validity of the method. This might represent a useful laboratory test for the early evaluation of therapy in advanced carcinoma.

### Clinical Significance of Proteolytic Activity in Blood

Under normal conditions, human plasma does not exhibit detectable proteolytic activity on a fibrinogen substrate. However, proteolytic activity may appear in the blood in certain diseases. Thus, fibrinolytic activity of the blood has been observed in shock due to trauma, hemorrhages, burns and so forth.[72] The first case of fibrinolysis in postpartum hemorrhage was reported in 1946[72] and was soon followed by other reports.[73, 74] This fibrinolysis causes fibrinogenopenia, although intravascular clotting rather than fibrinolysis has been incriminated by others.[75] That fibrinolysis was responsible in the first reported case cannot be refuted since direct in vitro demonstration of fibrinolysis in the patient's plasma was obtained.[72] Fibrinolysis in such circumstances may be just another result of hemorrhagic shock. How shock and anoxemia produce fibrinolysis is not explained.

There are activators of plasminogen in certain tissues,[76] especially in the lung[77] and the thymus.[78] It is possible that the state of anoxemia promotes activation of plasminogen through some mechanism similar to the activation by these tissue constituents. It was recently pointed out that fibrinolysis was frequent in surgical operations on the lungs,[79] and this was explained by the presence of a powerful plasminogen activator in lung tissue. Another study found the incidence of fibrinolysis not higher in lung operations than in any other type of operations.[78] There is a certain incidence of fibrinolysis in surgical operations, probably associated with the variable occurrence of transient anoxemia in extensive surgical procedures.[79] Fibrinolysis has also been observed in certain patients with cirrhosis of the liver[80] and, as discussed above, with cancer of the prostate.[66, 67] However, fibrinolysis remains a specific phenomenon, which is not seen except in shock, advanced liver disease and metastatic cancer of the prostate. It is possible that future observations will lead to its detection in association with other diseases.

When fibrinolysis is intense it produces a hemorrhagic condition characterized by a deficiency of prothrombin, accelerator globulin and fibrinogen and by weak and fragile clots.[66, 67] Mild and transient degrees of fibrinolysis, however, may exist without detectable impairment of hemostasis. The use of inhibitors of the fibrinolytic enzyme for therapeutic purposes is still experimental but appears promising.[67]

## Summary

There is evidence in the medical literature of a rapidly growing interest in the field of the clinical application of enzymes. Some of the recent developments are briefly discussed. The evaluation of the effectiveness of enzymes in therapy requires a knowledge of the fundamental principles of enzyme chemistry as well as the ability to evaluate correctly the results of clinical investigation.

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# MEDICAL INTELLIGENCE

## MID-THIGH AMPUTATION IN A PATIENT WITH HEMOPHILIA*


JOHN H. CRANDON, M.D.,†
LEONARD STAUDINGER, JR., M.D.,‡ AND
ELI FRIEDMAN, M.D.§

BOSTON


REVIEW of the literature on surgery in hemophilia reveals a liberal sprinkling of unauthenticated case reports. Nevertheless, it appears to be the general consensus at present that in this disease surgery should not be performed, particularly where the operative site will be inaccessible to local pressure dressings.[1] Thus, when a diagnosis of appendicitis has been made, the treatment is preferably medical.


*From the Pediatric Service and First Surgical (Tufts) Teaching Service, Boston City Hospital.

†Assistant professor of surgery, Tufts College Medical School; junior visiting surgeon, Boston City Hospital.

‡Resident, First Surgical Service, Boston City Hospital.

§Associate professor of pediatrics, Boston University School of Medicine; pediatrician-in-chief, Boston City Hospital.


The present case deals with a patient with proved hemophilia in whom a hematoma of the popliteal space developed, with resulting compromise of the circulation to the lower leg. Efforts to relieve the local pressure by incision of the popliteal fascia were of no avail, so that a mid-thigh amputation was ultimately performed.

### CASE REPORT

W.D., a 5-year-old boy, was admitted to the Pediatric Service of the Boston City Hospital on December 2, 1952, with the chief complaint of swelling of the right foot and leg of 24 hours' duration. The mother stated that 3 days previously a "cold" with a nonproductive cough had developed. Twenty-four hours before admission the right leg from the knee to the toes became swollen, slightly tender and held in a semiflexed position. There was no history of trauma.

A diagnosis of hemophilia had first been made at the age of 5 months, when a hematoma of the right thigh secondary to trauma had developed. Since that time there had been 16 admissions because of hemorrhage or hematoma secondary to trauma of the face, mouth, elbows, shoulders and thighs. At the age of 14 months a subdural hematoma followed a fall, after which there had been evidence of mental retardation.

There was known hemophilia in the mother's uncle, her brother and 2 first cousins (both males) of the patient.

Physical examination revealed a well developed and well nourished boy with evidence of mental retardation. Positive findings included slight redness of the pharynx and a swollen, tender, cold, mottled-purple right leg from knee to toes. There were no palpable popliteal dorsalis-pedis or posterior-tibial pulses of the involved leg. There were also several small ecchymotic areas on both lower limbs.

The urine was normal. Examination of the blood revealed a red-cell count of 2,650,000, with a hemoglobin of 4.5 gm. per 100 cc., and a white-cell count of 12,000. The bleeding time was normal (2 minutes), and the clotting time was 23 minutes (Lee-White method).

The patient was treated with elevation of the extremity, bed rest, and Gantrisin, 0.25 gm. 4 times daily. On the 2d hospital day the Surgical Service was called in consultation. At that time

the lower leg was swollen approximately 2½ times its normal size, was markedly tender to palpation, was mottled purple in color, with no pulses, and was held in a position of 45° flexion at the knee and marked plantar flexion of ankle and toes. The patient was taken to the operating room, where under ether anesthesia a small incision was made over the medial aspect of the popliteal space. About 5 cc. of old blood exuded from the popliteal space. No undue bleeding was noted. Further dissection revealed hemorrhage into the fascial planes and calf muscles of the lower leg. The popliteal artery was palpated and found to be pulsating. The wound was closed by a running lock suture of atraumatic No. 00 chromic catgut to the skin. The leg was wrapped in sterile sheet wadding and placed in a posterior plaster shell splint. Postoperatively the color of the leg and foot improved slightly, but only for a few hours. The patient was placed on procaine penicillin, 300,000 units daily, and priscoline, 10 mg. 3 times daily. About 12 hours after the operation the popliteal wound began to ooze, so that frequent reinforcements of the dressing were required. Transfusions of fresh whole blood were given daily. On the 3d day the oozing ceased. At this time the lower leg to the ankle was warm and of good color, but the foot was cold and mottled. Neither the posterior-tibial nor dorsalis-pedis pulses could be palpated at any time. Several bullae appeared along the posterior aspect of the calf during the next 2 days. On the 6th day, because of elevation of temperature to 104°F., chlortetracycline therapy by mouth was begun, 100 mg. every 6 hours being given. The leg was placed in a position of moderate elevation, since the color of the foot was improved thereby.

On the 11th day the 2d toe appeared black and gangrenous. This process slowly spread to include all the toes. A sloughing area developed on the posterior aspect of the calf at the lower end of the popliteal incision. The temperature continued to be elevated, ranging up to 104.5°F. on the 16th day. The white-cell count was 24,000, and the clotting time was 18 minutes. The entire foot was gangrenous, and the lower leg was badly discolored (Fig. 1). A "cut-down" was placed in the left ankle, and a mid-thigh amputation was performed. Again, no undue bleeding was seen at operation. The wound was closed without drainage, No. 000 atraumatic chromic catgut being used for the fascia and No. 36 stainless-steel wire sutures for the skin. A fluff-gauze dressing with superimposed elastic-bandage pressure dressing was applied; 1000 cc. of fresh whole blood was administered during the course of the operation. The clotting time was 9 minutes.

FIGURE 1. *Appearance of the Leg Eighteen Days after Admission and Seventeen Days after Incision of the Popliteal Fascia.*

The stump dressing began to stain fresh blood at the end of 6 hours after operation. Oozing from the stump continued for the next 3½ weeks. Fresh whole-blood transfusions in the amount of 200 to 500 cc. were given daily. Dressings were changed every 2 days. At the end of the 2d week the "cut-down" wound in the opposite leg also began to ooze. This was finally controlled after 4 days by a running suture of fine silk and increased pressure to this area. The patient's temperature gradually returned to normal on the 9th postoperative day, remaining normal for the remainder of his hospital stay. Chlortetracycline was omitted and penicillin begun. During the postoperative period the clotting time ranged between 4 and 16 minutes. At the end of the 2d week, low-grade sepsis developed in the medial aspect of the amputation wound. At this time marked ecchymosis of the upper thigh, groin and perineum was noted. Wet saline dressings were applied to the stump. There was a gradual subsidence of sepsis and 5 weeks after the operation the sutures were removed. Several small granulating areas in the wound were cut down and treated with silver nitrate. On the 69th postoperative day and the 92d hospital day, the patient was discharged on crutches to be followed in the Outpatient Department, where a suitable prosthesis was to be fitted.

## DISCUSSION

The first successful amputation in a case of proved hemophilia was reported by Blalock[2] in 1932. At this operation a mid-humeral amputation was performed in which every bit of tissue was ligated separately with the exception of skin and bone. Tannic acid was sprayed into the open wound, which was packed open with a pressure dressing. Firor and Woodhall[3] successfully amputated the thumb of a patient with known hemophilia with the use of an electrocautery in 1936.

The case reported above meets the criteria for the diagnosis of hemophilia as postulated by Craddock, Fenninger and Simmons[1] as follows: a clotting time of 20 minutes or longer; a positive family history; a typical past history; occurrence in a male.

The inability to relieve the embarrassment of the circulation in the lower leg of this patient by incision of the popliteal fascia is noteworthy. In contradistinction to what might be expected in the normal person, the offending hematoma was not confined to the popliteal space, but was found to be diffusely infiltrating the calf muscles of the lower leg as well. This was confirmed by dissection of the limb after amputation. No definite bleeding point could be discovered. Identical findings were described in 1856 by Erichsen,[4] who reported a similar case that ultimately required mid-thigh amputation, with a fatal termination.

Noteworthy also was the fact that this patient's wound continued to ooze, even when the clotting time had been reduced to normal by repeated transfusions with fresh whole blood. This observation has been emphasized by Craddock, Fenninger and Simmons.[1] The ability to apply local pressure to this patient's wound was undoubtedly the determining factor in the outcome. It is apparent that in hemophilia hematomas of fascial spaces of the extremities are apt to be diffuse so that relief of pressure by local drainage is unlikely to succeed.

## SUMMARY

A mid-thigh amputation in a proved case of hemophilia is reported. Incision of the popliteal fascia to relieve tension caused by a hematoma had

been unsuccessful. Postoperatively local pressure, as well as repeated fresh whole-blood transfusions, appeared to be a crucial factor in the successful outcome.

We are indebted to Dr. Frederick Bigelow, of the Thorndike Memorial Laboratory, for his kind advice and assistance in this case.


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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises


FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*


## CASE 39421

### PRESENTATION OF CASE

*First admission.* A seventy-three-year-old retired mechanic was admitted to the hospital because of a mass in the lower abdomen.

For about a year before admission the patient had noted increasing tightness when buttoning his trousers, and a sensation of fullness in the lower abdomen and in the right flank. The mass was otherwise asymptomatic.

He had had no operations. Twenty years previously he "passed gravel" in his urine. There was no history of dysuria, nocturia, pyuria or hematuria. During the day he urinated about once every hour and a half.

On examination the patient appeared healthy. A soft, rounded mass, dull to percussion, occupied the lower abdomen and right flank. Bleeding hemorrhoids were noted, and the prostate was found to be small, uniform and freely movable. The abdominal mass seemed very soft, and could not be outlined by rectal palpation.

The temperature was 98.4°F., the pulse 72, and the respirations 24. The blood pressure was 135 systolic, 88 diastolic.

The urine was cloudy and acid, and had a specific gravity of 1.006; it gave a + test for albumin; the sediment contained 30 red cells and occasional white cells per high-power field. The blood hemoglobin was 15.1 gm., the serum nonprotein nitrogen 32 mg., the fasting blood sugar 106 mg., the total protein 6.95 gm., the albumin 5.00 gm., and the globulin 1.95 gm. per 100 cc. The prothrombin time was 13 seconds (normal, 15 seconds). An electrocardiogram showed prolonged QRS complexes and abnormal T waves consistent with coronary-artery disease. A roentgenogram of the chest was normal except for slight prominence of the heart and slight sclerosis of the aortic arch. A barium-enema examination demonstrated a large, extrinsic, hard, smooth mass rising out of the pelvis, displacing the sigmoid colon outward and posteriorly, and the ascending colon anteriorly and medially. Small oval calcifications were observed within the mass. An intravenous pyelogram revealed no filling on the right, and marked hydronephrosis on the left.

When catheterization was performed on the fourth hospital day, a definite resistance was encountered in the posterior urethra. After 1350 cc. of residual urine was drained, the pelvic mass disappeared but the mass in the right flank remained. An indwelling catheter was placed, and two days later the right-flank mass also diminished in size. A phenolsulfonephthalein test performed at this time showed 60 per cent excretion in one hour and 80 per cent at the end of two hours. On the eleventh hospital day the patient had a mild febrile episode associated with tenderness in the right flank and costovertebral angle. The white-cell count was 5500. A urine culture grew out *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*). After four days of treatment with penicillin and streptomycin, the fever and tenderness subsided. A transurethral resection was performed on the nineteenth hospital day. The pathological report was benign prostatic hypertrophy.

He was discharged on the thirtieth hospital day.

*Second admission* (six months later). He was readmitted to the hospital for further study because he had been unable to void and had been on continuous catheter drainage since the transurethral resection.

The physical findings were unchanged since his discharge.

The temperature was 98.0°F., the pulse 72, and the respirations 20. The blood pressure was 130 systolic, 70 diastolic.

The urine had a specific gravity of 1.014 and gave a ++ test for albumin; the sediment was

oaded with white cells. The blood hemoglobin was 14.0 gm., and the white-cell count 7100. Urine culture yielded colon bacilli.

A partial cystectomy to diminish the bladder capacity was considered, but since cystoscopy, panendoscopy and a cystogram showed some decrease in bladder size, continued conservative management was decided upon. At the time of discharge he was still on continuous catheter drainage. Subsequently he voided well and emptied his bladder.

*Third admission* (fourteen months later). He was readmitted to the hospital because of bloody urine for four weeks.

His progress after the last hospitalization had been satisfactory until he noted hematuria. He

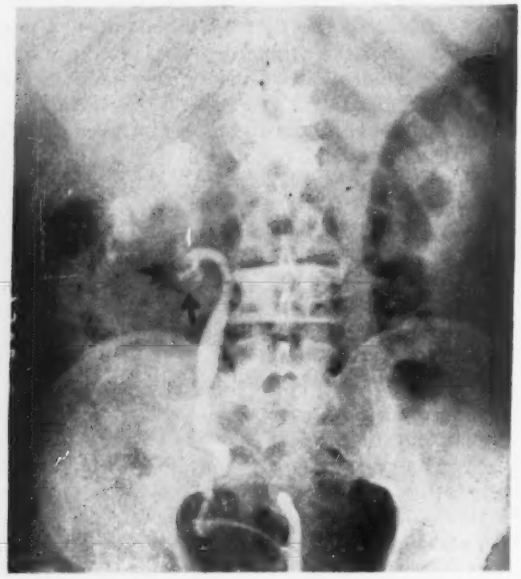

FIGURE 1. *Roentgenographic Examination, Showing the Filling Defect in the Upper Ureter and Pelvis of the Right Kidney. Note the sclerosis of the fourth lumbar vertebra and sacrum.*

continued to feel well, but lost 8 pounds in weight during the month preceding admission. An intravenous pyelogram performed two weeks before admission was reported as showing that the left urinary tract was essentially normal, and that the right kidney apparently had no visible function.

The physical findings were not changed. The kidneys were not palpable.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 140 systolic, 90 diastolic.

Urinalysis and routine hematology were unchanged since the last admission. The sediment was loaded with white cells but did not contain red cells.

A cystoscopy and right retrograde pyelography were done the day after admission. The bladder urine was very cloudy and grossly infected. After the bladder had been washed, it showed a little redness but nothing very abnormal. Both ureteral orifices were extremely obscured. Indigo carmine given intravenously appeared in the same concentration bilaterally only after about fifteen minutes. At no time was the dye very dense. It was not possible to see where the dye was coming from, but eventually the right ureteral orifice was found high on the bladder base. A catheter could be passed only for a short distance. The pyelogram outlined a tortuous right ureter, which showed a sharp kink at the ureteropelvic junction. There was considerable irregularity of the right ureter in its most proximal portion. The calyxes were not completely filled, and those that were filled were dilated and irregular in outline. The right renal shadow could not be outlined peripherally, and the psoas-muscle shadow was not seen on that side. There were small calcifications in the right flank that apparently lay within the hydronephrotic kidney. There were definite changes in the skeleton since the previous x-ray examination — increased density of the fourth lumbar segment and along the medial aspect of the right ilium (Fig. 1).

On the fifth hospital day an operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR. GEORGE G. SMITH*: "Both ureteral orifices were extremely obscured." This sentence is also obscure. Does it mean that the orifices could not be recognized, that they were hidden behind the prostate or something else? How were they obscured? Another point I wondered about is, How did the physicians know that the indigo carmine appeared in the same concentration bilaterally if they could not see from which ureter it was coming? Dye often swirls around the bladder and gives the impression that it is coming from one side even in a case in which there is no ureter on that side. Intravenous pyelograms had shown that the left kidney was functioning, however, but not the right.

This long history may be boiled down to two or three main features. Among the less important positive findings is the overdistended bladder that the patient had when he first came in. After the transurethral resection and catheter drainage, however, for at least seven months the patient voided well and emptied the bladder so I think that the distention of the bladder was not particularly important.

*Member, Board of Consultation; formerly, chief, Urological Service, Massachusetts General Hospital.

Much more important in the diagnosis, I think, is the fact that there was a mass in the right flank at the first admission that decreased in size after the bladder had been drained for two days but evidently was still palpable. That the mass took two days to diminish in size suggests that the outflow from the right kidney was very much hindered, and that was shown by dilatation of the calyxes and the fact that the kidney no longer demonstrated any appreciable function when an attempt was made to take an intravenous pyelogram. Twenty months later neither kidney was palpable so that the mass in the region of the right kidney was almost certainly due to retention of urine that gradually leaked out into the ureter, reducing the kidney to its normal proportions.

Why was there hematuria? This was not noted until the third admission, twenty-one months after the first admission. In the intravenous pyelogram at this time the left ureter and kidney were normal, but the right kidney still showed no function. Cystoscopy during the third admission revealed no stone or tumor in the bladder and no obvious source of hematuria. The ureters were difficult to identify, but eventually the right ureteral orifice was noted very high on the bladder base. There are two possible explanations for this; the most likely is that the ureter had been shrunken in length by some process, such as tuberculosis, with which it occurs most often. In this case contraction of fibrous tissue about the ureter may have pulled the ureteral orifice into quite a high position on the bladder base. A less likely possibility is that a tumor or mass of some sort behind the trigone had pushed the trigone up — but nothing of that sort was found on rectal examination. A ureteral catheter passed only a short distance into the right ureter. Although that is sometimes due to a kink in the ureter that is not pathological, it seems in this case it could be better explained by something else. A retrograde pyelogram was done so that the ureteral lumen was patent enough to allow fluid to pass up to the kidney pelvis; however, although it did not show complete filling of the pelvis or calyxes, there was dilatation and irregularity of such calyxes as were visible. The upper portion of the ureter was quite irregular and sharply kinked at the ureteropelvic junction. The outline of the right kidney was not demonstrated, and the shadow of the right psoas muscle was not seen. There were changes in the fourth lumbar vertebra and right ilium suggestive of metastatic carcinoma. Dr. Wyman, may I see those films? The retrograde pyelogram should be the most important one.

Dr. Stanley M. Wyman: The plain film of the abdomen on the first admission shows areas of indefinite soft-tissue fullness in the lower abdomen and in the right flank. This is probably a gallstone shadow in the right flank. The pyelogram reveals greatly diminished renal function; the sixty-minute film shows gross dilatation of the calyxes and pelvis of the left kidney and no excretion by the right kidney.

Dr. Smith: That was before the bladder had been drained?

Dr. Wyman: Yes; that was before the initial operation had been done. On the same day a barium-enema examination demonstrated a much distended bladder pressing upon the sigmoid and rectum and a mass in the right flank pressing upon the cecum and ascending colon. There are at least 4 or 5 rather rounded calcifications in the mass, and these change somewhat in position from film to film. A gastrointestinal series shows displacement of the bowel by this mass in the right flank but nothing more than that. An intravenous pyelogram done a few months later, and not referred to in the history, reveals function on the right side and on the left. The right ureter is greatly dilated, and in view of the later history one wonders about a kinking and possibly a filling defect in the proximal ureter. A small calcification, which was previously low in the abdomen, now lies higher, suggesting that this kidney has decreased in size. The next films demonstrate the sclerosis of the body of the fourth lumbar vertebra and of the right side of the pelvis that, as Dr. Smith has said, is consistent with metastatic carcinoma. An intravenous pyelogram now shows no definite function of the right kidney and a grossly normal left kidney. In the last films from the retrograde examination there is irregularity in the proximal ureter on the right, with a filling defect extending into the kidney pelvis. This corresponds quite closely to the area noted on the previous intravenous pyelogram.

Dr. Smith: I am somewhat disappointed in these pyelograms; I thought I should see much more distention and irregularity of the right ureter; however, I think there is enough to give me a toehold on a diagnosis.

Interest centers in the right kidney, which was without function but was dilated as if by obstruction to drainage. The ureter was irregular and kinked according to the history and admitted the catheter for only a short distance. The reason the catheter failed to pass beyond this point was probably that, as sometimes happens, there was a sharp bend in the ureter rather than a true intrinsic closure or stricture of the ureteral lumen. The hematuria, for which no cause could be found in the bladder, might well be assumed to have come from the right ureter. The psoas muscle was well seen on the left and not on the right. Several years earlier, two years before the last admission, the psoas muscle was visible on both sides. Obliteration of the psoas-muscle shadow is a very important point in the detection of perirenal infection — perhaps a perinephritic abscess — situated at the lower pole of the kidney, or of a tumor overlying it in the iliac fossa.

I should explain the outstanding symptoms in this patient's case as being due to an obstruction of the right ureter immediately below the renal pelvis. The nature of that obstruction might be inflammatory, but because it had persisted for so long, because the psoas muscle was overlain and its edge was obscured, because there was blood coming from the ureter and because there were changes in the bone, I shall make a diagnosis of carcinoma of the upper end of the ureter that was obstructing drainage from the kidney and was the cause of these symptoms.

Dr. Thomas F. Paine: Were acid-fast bacilli found in the urine?

Dr. Edgar B. Taft: I do not believe any search was made for them.

Dr. Fletcher H. Colby: There was never anything to suggest tuberculosis in this case. We thought this man had a thoroughly infected hydronephrotic right kidney damaged by long-continued chronic pyelonephritis. A right nephrectomy was done with considerable difficulty because the perirenal tissues were very adherent to the kidney, which as I remember it was not large. The upper portion of the ureter only was removed.

### Clinical Diagnosis

Infected hydronephrosis.

### Dr. George G. Smith's Diagnosis

Carcinoma of ureter, with constriction.

### Anatomical Diagnoses

*Squamous-cell carcinoma of renal pelvis, with extension to ureter.*

Chronic pyelonephritis, marked.

### Pathological Discussion

Dr. Taft: The specimen that we received was a kidney accompanied by a large amount of attached perirenal fat. The pelvis, calyxes and ureter were markedly dilated, and the kidney substance was markedly decreased in amount, in some areas to a thin shell. The mucosa of the pelvis was rough, granular and markedly thickened. The capsule was firmly adherent to the kidney substance. The surrounding fat had focal, firm areas, but no lymph nodes could be found in the specimen. The renal vessels were not abnormal.

Microscopically, there was a typical squamous-cell carcinoma of the renal pelvis that, as far as we could tell, was of pelvic origin, but it could just as well have been ureteral. It involved both, although it involved the ureter to a lesser extent than one would expect if it had been primary there. This tumor had invaded the lymphatics of the tissue surrounding the kidney, and small islands of tumor could be found in the perirenal fat. There was an incidental rib accompanying this specimen that Dr. Colby asked us to examine carefully for metastatic tumor; we found several small foci of metastatic squamous-cell carcinoma in the bone marrow of the rib so that almost certainly the masses seen in the bones elsewhere represented metastatic carcinoma.

Dr. Paine: How do you explain the large mass that appeared at one point and then disappeared?

Dr. Taft: I think Dr. Smith's explanation of it is correct in that once drainage was established in the urinary tract, the kidney greatly decreased in size.

A Physician: How do you explain the calcification?

Dr. Taft: There was a tremendous amount of infection in the residual kidney parenchyma with some calcification, and I suspect that the calcified spots seen radiologically were foci of calcification within the kidney parenchyma.

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## CASE 39422

### Presentation of Case

*First Admission.* A seventy-four-year-old retired insurance agent entered the hospital because of low-back pain and constipation.

About fifteen years before admission the patient began to notice palpitation of the heart and heaviness in the arms and legs. Four years later he had several "sinking spells," and examination revealed a rare cardiac extrasystole; the blood pressure was 145 systolic, 90 diastolic. Eight years before admission the blood pressure was 160 systolic, 100 diastolic, and the heart was fibrillating. The fibrillation persisted to the time of admission, and he had been digitalized ever since, although he was never in cardiac failure. About two and a half years before admission he had a respiratory infection, associated with a productive cough and an area of diminished breath sounds with rales found at the left lung base. About a year later a roentgenogram revealed an elevated left leaf of the diaphragm and a small amount of fluid in the left pleural cavity, with some irregular density above the fluid. This finding persisted, but he did well until about four months before admission, when he had a sudden attack of sharp pain in the precordial area radiating to both sides of the chest and left shoulder. His physician gave him nitroglycerin; the pain subsided the next morning and did not recur. A few days later, his bowel movements changed from the usual two or three times a day to once every four or five days. The stool was hard and was not associated with blood. The constipation persisted. Shortly afterward, he started to have severe pain in the lower back. It had occasionally awakened him at night and was exaggerated by standing, jarring the back and straining at stool, and was relieved by lying down. Since then he had felt considerably weaker and had lost about 10 pounds in weight.

Physical examination revealed a moderately well preserved man with signs of moderate recent weight loss. There were dullness, diminished breath sounds, fine rales and egophony in the left-lung base and axilla. The heart was enlarged, with the left border 13.5 cm. from the midsternal line. The cardiac rhythm was irregular, and there was a Grade 3 systolic murmur at the apex. The pulmonic second sound was louder than the aortic. The abdomen was normal. Rectal examination revealed a relaxed sphincter. There was no peripheral edema.

The temperature was 100°F., the pulse irregular at a rate of 80 per minute, and the respirations 20. The blood pressure was 188 systolic, 110 diastolic.

The urine had a specific gravity of 1.019 and gave a ++ sugar reaction; the sediment contained 5 to 7 white cells and occasional casts per high-power field. Examination of the blood showed a hemoglobin of 13 gm. per 100 cc. and a white-cell count of 10,000, with 68 per cent neutrophils, 24 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. The hematocrit was 46 per cent. The sedimentation rate was 1.4 mm. per minute. The fasting blood sugar was 152 mg., the total serum protein 6.8 gm., the albumin 4 gm., the globulin 2.8 gm., the alkaline phosphatase 4.4 units, the calcium 9 mg., and the phosphorus 3 mg. per 100 cc. A stool guaiac test was negative, as was a cytologic examination of the sputum. An electrocardiogram disclosed auricular fibrillation at a rate of 70 to 80 per minute, a QRS interval of 0.08 second and a normal axis. The R waves were absent in Leads $V_1$ and $V_2$ and tall in Leads $V_4$ and $V_5$, the S waves deep in Lead $V_2$, the ST segments depressed in Leads 1, 2, aVF, $V_2$, $V_4$, $V_5$ and $V_6$, and the T waves diphasic in Leads 1, 2, 3 and aVF and inverted in Leads $V_4$, $V_5$ and $V_6$.

A roentgenogram of the chest demonstrated further evidence of consolidation and collapse in the left lower lobe as compared with a film taken one and a half years before admission; the diaphragm was not visualized at fluoroscopy but appeared to move satisfactorily; a small amount of fluid in the left costophrenic angle could not be excluded; the left ventricle appeared slightly larger than before. A barium-enema examination was negative. Films of the lumbar spine showed moderately severe osteoporosis; the pelvic bones were also osteoporotic, but there was no evidence of bone destruction. An intravenous pyelogram revealed that the right kidney was normal in size, shape and position, but the right renal pelvis and calyxes were displaced somewhat downward; the left kidney was lower than the right and had an irregular outline. A repeated pyelogram again showed a low left kidney, but there was no evidence of a mass displacing it.

Further examination of the patient after admission revealed no muscular spasm and no evidence of nerve-root injury. Examination by the urologist demonstrated a small, irregular, compressible prostate, with an area of increased firmness on the right side that was thought to be fibrosis. The patient was given digitalis, diabetic diet, sedatives, stilbestrol and methyl testosterone and was put in a body jacket. He was discharged sixteen days after admission.

*Final admission* (two months later). He was seen in the clinic two weeks after the discharge, when the body jacket was removed. He appeared much improved and there was no tenderness or muscle spasm of the back. He was seen again eighteen days later in a similar status. Two weeks before entry the abdomen started to swell, and in the last four days, it had "ballooned up." One week before admission, he began to lose appetite and became restless but very sleepy. Four hours before entry, he began to vomit copious amounts of black-brown material. There was no pain.

On examination in the Emergency Ward he was cachectic and stuporous, with minimal nail-bed cyanosis. A harsh systolic murmur was heard at the apex of the heart. There was ascites. The blood pressure was 60 systolic, 40 diastolic. The pulse was irregular at a rate of 110 per minute. He died twenty minutes after admission.

## Differential Diagnosis

Dr. John B. Stanbury*: Was a determination of the acid phosphatase of the serum made?

Dr. Benjamin Castleman: No; it was not.

Dr. Stanbury: One of the most satisfactory ways to approach a clinicopathological conference is to build the case around a single particular abnormal finding. I find no such abnormality in this protocol around which to build my case. Perhaps the x-ray films will help.

Dr. Stanley M. Wyman: The original films of the chest a year and a half before death show the elevation of the left leaf of the diaphragm as reported in the protocol. There is some pleural reaction, which may be fluid or thickening of the pleura. There is slight reduction in size of the basal segment of the left lower lobe chiefly involving the anterior, medial and lateral portions — not so much the posterior basal portion. The heart shadow is considerably enlarged in the region of the left ventricle, and the aorta is tortuous, with calcification in its wall. The chest is slightly emphysematous, which is not unusual for a man of seventy-four years. The bones are demineralized, and there are degenerative changes.

Dr. Stanbury: For a man of seventy-four would you say the bone changes are striking?

Dr. Wyman: I think they are about average for a man of that age. The bones of the spine as seen on later films show a more striking degree of demineralization. There is some wedging, some narrowing, of the upper lumbar or perhaps the lowermost thoracic vertebra, but I do not see any localized

*Assistant physician, Massachusetts General Hospital.

bone destruction. The barium-enema examination of the colon gives no evidence of an intrinsic abnormality.

DR. STANBURY: I am not told where the pain was; would it be fair to ask whether it was a generalized pain over the whole back or a sharply localized pain?

DR. ALEXANDER LEAF: It was midlumbar.

DR. STANBURY: Do you see any localized areas of bone destruction or just generalized demineralization?

DR. WYMAN: I cannot find any of the small rarefactions that we might hope to see in myeloma, but we know that demineralization alone may occur in that disease. The films from the two intravenous pyelograms show the position of the left kidney to be consistently lower than the right (the left kidney is normally higher than the right); despite the fact that the left leaf of the diaphragm is higher than usual, the left kidney is lower than usual. Secondly, the calyceal system of the left kidney lies somewhat vertically. However, I cannot see any intrinsic distortion of the calyxes of either kidney. I cannot say much about the reported irregularity of the left kidney, which seems insufficient to warrant my saying that there is an intrinsic abnormality there.

DR. STANBURY: Is the liver normal in size?

DR. WYMAN: I think the liver is average in size. I am sorry that the last two examinations of the chest do not include the posteroanterior films that were taken. It is clear that the process involving the basal segments of the left lower lobe has increased in density. There is a considerable decrease in size of the basal segments of the left lower lobe, with a mass in that portion of the lung.

DR. STANBURY: Are the hilar lymph nodes normal as far as you can tell?

DR. WYMAN: I cannot tell that from these lateral films alone, but I cannot see any real lymph-node enlargement on the original films.

DR. STANBURY: The discussion of this protocol might open with a few remarks about several organ systems. Perhaps we know most about the heart. This patient clearly had heart disease. It may have been heralded eleven years before admission by "sinking spells," which conceivably were transient bouts of auricular fibrillation or some other cardiac irregularity with fainting episodes. Eight years before death hypertension was found, becoming worse as the years went by. At that time auricular fibrillation became established and continued until the patient's death. At the time of the first admission a loud systolic murmur was heard at the apex of the heart. Whether this was the murmur of mitral regurgitation or whether it was associated simply with a dilated arteriosclerotic heart I have no way of knowing. The electrocardiogram does not help me very much. It revealed the findings of left-ventricle hypertrophy and the nonspecific changes of an arteriosclerotic heart. It is perhaps consistent with a previous myocardial infarct. The precordial pain radiating to both shoulders and down the left arm that the patient experienced four months before admission may have been left-ventricle strain or a small myocardial infarct. Did the ascites that suddenly developed a few days before he died have anything to do with the heart? Certainly, ascites occurs with congestive heart failure, but usually in association with edema elsewhere; I am much inclined to the opinion that this ascites had an origin other than simple congestive heart failure and that the patient had hypertensive and arteriosclerotic heart disease that did not contribute to his death.

Other prominent features in this patient's illness were back pain and osteoporosis. As seen in the x-ray films, the osteoporosis was much more severe in the lower spine and in the pelvis than in the bones of the thorax and upper extremities. How much more osteoporosis was present than is found in a sedentary seventy-four-year-old patient I am sure I do not know. Nor can I be certain that it had anything to do with the back pain. The pain could have been due merely to osteoporosis with slight wedging of the vertebras, or perhaps to an unrelated lesion — for instance, a metastatic lesion or a primary tumor of the spinal cord. The pain was exaggerated on straining, which might have elevated the cerebrospinal-fluid pressure. It is difficult or impossible to make a diagnosis of primary or metastatic cancer of the spine in the absence of positive neurologic findings, positive x-ray findings or spinal-fluid examination.

Among other problems were a disorder of bowel function and ultimately development of ascites. Beginning shortly before the first admission he had a distinct change in bowel habit, from normal to only one movement every four or five days. This change was clearly not due to obstruction of the lower bowel because the barium-enema examination was entirely negative. Such distinct changes in bowel habit certainly can occur from the develop-

ment of either a benign or a malignant lesion in the stomach or bowel. Constipation is not uncommon in patients with carcinoma of the stomach and even in patients with a duodenal ulcer. It surprises me that during the sixteen days in the hospital no gastrointestinal series was taken. Carcinoma of the stomach can give many of the signs and symptoms that this patient demonstrated, but in the absence of that examination and without ancillary data I cannot make that diagnosis.

Shortly before death ascites developed. There is no evidence from the protocol that the patient had liver disease. It is therefore impossible to attribute the ascites to liver disease. To what else could it have been due? I have already ruled out congestive heart failure. I believe he had an infectious or a malignant seeding on the peritoneum, and perhaps a block to return of blood from the portal system either in the portal vein or in the hepatic vein. If the block was at the hepatic vein, he would have had Chiari's syndrome, but he did not because he had no pain, no enlargement of the liver and no high fever. It is quite possible that there was thrombosis or invasion by cancer, or both, of the portal vein. The pulmonary lesion may have been atypical tuberculosis. The ascites could then have been caused by peritoneal spread.

The patient had diabetes. This was discovered at the time he was first admitted and was mild and easily controlled. The terminal episode is suggestive of diabetic acidosis. He vomited copious amounts of black-brown material and was admitted in shock. Of course we do not know whether or not any of the other clinical findings of diabetic acidosis such as Kussmaul breathing were seen. One may well suspect that the terminal episode was diabetic acidosis into which the patient had been tipped by the underlying disease that precipitated the vomiting. Nothing makes diabetic acidosis progress faster than vomiting.

Finally, the patient had pulmonary disease. Two and a half years before admission there was a so-called respiratory infection. From that time until the final examination there was a slowly progressive disease, which caused a collapse of the left lower lobe, cough and sputum. Only one sputum examination was performed, and that one failed to show tumor cells. One must consider the possibility that the mass and the collapsed lower lobe were due to a carcinoma of the lung, which in the latter days of the patient's life metastasized widely or perhaps extended through the diaphragm to interfere with venous return to the liver, thereby accounting for the ascites and death.

Certain other possibilities must be mentioned before closing. Was there metastatic disease of other origin? Carcinoma of the pancreas can be extremely silent; however, the pain was not like that which one ordinarily finds in pancreatic carcinoma, and there is no other reason to make that diagnosis. The mass in the left upper quadrant could have been pancreas or an enlarged spleen. We must consider, as Dr. Wyman mentioned, multiple myeloma, which could account for the renal findings, the osteoporosis, and some of the other symptoms, but in the absence of albuminuria and localized bone disease I do not think I can rationally make a diagnosis of multiple myeloma. We must also consider primary renal neoplasm on the left side, but that diagnosis cannot be made on present evidence.

The patient surely must have had hypertension and coronary-artery disease. I shall also make a diagnosis of carcinoma of the lung that had metastasized and perhaps extended downward to prevent, in some way, venous return to the liver, thereby causing ascites, and possibly exudation into the stomach and bloody vomitus. I wonder if the terminal episode was not complicated by diabetic acidosis.

DR. JOSEPH C. AUB: Would you consider a neoplasm in the stomach?

DR. STANBURY: I do not know. If the portal vein is occluded suddenly, is there bleeding into the stomach?

DR. CASTLEMAN: I do not recall having seen that.

DR. AUB: The spleen was not enlarged. The large bowel extends high on the left, which it would not if the spleen were enlarged.

DR. WYMAN: I should agree with Dr. Aub.

DR. REED HARWOOD: It seems to me that with the rapid onset of ascites in the last week of life one would not have to postulate diabetic acidosis to explain the vomiting. I should think it was vomiting from esophageal varices secondary to thrombosis of the portal vein.

DR. CASTLEMAN: Thrombosis of the portal vein due to what?

DR. HARWOOD: Cancer of the pancreas, or in the lung. I should put the pancreas first; however, I cannot explain the lesion of the lung on that basis.

DR. STANBURY: I had thought of the black vomitus as being the type seen in patients with diabetic acidosis.

DR. AUB: Diabetic acidosis is a very good diagnosis to make; the pathologist cannot say whether it is right or wrong.

DR. STANBURY: I hope that blood for chemical determinations was drawn before the patient died. He lived only twenty minutes after he came into the hospital.

DR. CASTLEMAN: No chemical studies were done.

### CLINICAL DIAGNOSIS

Coronary-artery disease.
? Carcinomatosis, with metastases to liver.

### DR. JOHN B. STANBURY'S DIAGNOSES

Carcinoma of lung, with metastases and extension.
Diabetic acidosis.
Hypertension and coronary-artery disease.

### ANATOMICAL DIAGNOSES

*Adenocarcinoma of lung, left lower, with metastases to pleura, peritoneum, liver, and vertebras.*
Coronary sclerosis with recent thrombosis.
Cortical cysts of kidney.
(Diabetes mellitus.)

### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy confirmed many of Dr. Stanbury's diagnoses. The heart was slightly enlarged, and there was severe disease of the coronary arteries; as a matter of fact we found in one of the coronary arteries a fairly fresh thrombus that probably was associated with the terminal episode. There was a great deal of scarring throughout the myocardium, which is to be expected with long-standing coronary-artery disease. There was no evidence of heart failure.

An adenocarcinoma involved the bronchus to the left lower lobe, which was shrunken and quite solid and, as was predicted, adherent to the diaphragm. There were tumor nodules extending through the diaphragm on the left side, numerous implants over the pleural surface and a tremendous number of implants in the abdomen that I believe caused the 8 liters of ascitic fluid found at the time of autopsy. There was no involvement of the vena cava or portal vein. The liver had a few metastatic nodules but was not enlarged, and I doubt if the nodules contributed to the ascites. The kidneys showed no involvement with tumor, but the right kidney had a large cortical cyst measuring 5 cm. in diameter that may have accounted for that first x-ray report that the right kidney was pushed downward. We found a few small cysts in the left kidney but the only thing that might have accounted for the changes in the left upper quadrant were the tumor nodules that were located on the surfaces of the pancreas and spleen. All the lumbar vertebras showed severe involvement with carcinoma. We found no cause anatomically for the diabetes. There was neither hyalinization of the islands of Langerhans nor tumor involvement of the pancreas.

DR. STANBURY: What was in the gastrointestinal tract?

DR. CASTLEMAN: We found some dark material in the stomach that I think was old blood. There were numerous tumor nodules on the serosa of the stomach, some of which had invaded the wall of the stomach and might have produced sufficient irritation of the mucosa to account for the vomiting.

DR. STANBURY: I still think this patient had diabetic acidosis.

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## WATER-POLLUTION CONTROL

ONE of the tragedies of man's occupancy of the globe on which his primordial seed happened to light in its drift through space has been the way in which he has plundered the earth's natural resources and the misuses to which he has put its topographic facilities.

Not the least of these depredations has been the centuries-old interference with the natural functions of streams and rivers, compounded by an almost universal contamination of their content. The natural function of rivers is to carry an excess of surface water to the sea, bearing a certain amount of top soil with it, for the surface of the earth is undergoing constant change independently of man's destructive efforts and regardless of his attempts at control.

It is natural that rivers should overflow at certain seasons and shrink into their channels at others; it is man's folly that he has denuded drainage areas so as to increase the precipitateness and extent of floods and accelerate the erosion of the land; it is his perversity that makes him build his cities on the banks of rivers and resent the overflow that floods him out.

Particularly inexcusable has been the large-scale pollution of the almost priceless commodity of free-flowing water, both through the chemical wastes of industry and by means of human excreta, wherever man, the great polluter, has settled adjacent to a stream. This indifference to consequences is not new, nor has it any racial, political or geographic limitations; as man has increased so has the problem grown, and only within recent years have any extensive efforts been made to correct the evil.

Significant among these efforts is New York's pollution-control law enacted as recently as 1949, with the long-range program of eventually decontaminating, to reasonable degrees, the state's 70,000 miles of stream and 3,500,000 acres of inland water. The program was initiated with surveys of existing conditions and the gradual classification of the areas of the State. Already actual control programs have been undertaken in 23 drainage basins, covering 8800 square miles.

To the extent that man can clean up after himself and undo the nuisances that he has committed, and to some degree conserve earth's natural resources, he can justify his continued tenancy of an earth where once nature maintained its own balances.

## MEDICAL SCHOOLS AT MIDCENTURY

THE quality of American medical education greatly improved in the first half of the twentieth century. This improvement in quality, accompanied at first by a relative decline in quantity, was especially noticeable during the 1920's and 1930's. During World War II the process was reversed: the quantity of doctors rose and the quality of their education ebbed. This was intended to be but a temporary reversal of what has now been a forty-year trend, but it brought into action forces and policies that challenged the maintenance of the

general ratio of physicians to population. This ratio has been fairly constant during the past thirty years. In 1920 there was 1 physician for every 729 persons; in 1950 there was 1 for every 720. Nevertheless, there are those who believe that more doctors are needed regardless of the quality of their training. It is perhaps significant that the advocates of quantitative expansion have been generally those who also favored substantial tax subsidization of medical education.

In 1947 the American Medical Association and the Association of American Medical Colleges joined together, with assistance from the Kellogg Foundation, to initiate what is undoubtedly the most careful and detailed survey of medical education that has ever been completed. The formal report of this survey, published by McGraw-Hill, was released in August under the title *Medical Schools in the United States at Mid-Century*.[1] The authors of this book are the director of the study, Dr. John E. Deitrick, professor of medicine at Jefferson Medical College, and his associate director, Dr. Robert C. Berson. Their report is based on the detailed study of 41 medical schools, supplemented by additional information from all the 79 medical schools in the country.

The report indicates that medical schools find themselves in their present financial difficulties in part because they originally assumed — or had thrust upon them — the obligation to participate in the education and training of many of the members of the nursing profession and a growing body of health workers. Even though schools of public health gradually assumed their own burden, today's obligations still include the instruction of nurses and many technical students. An even greater liability is the cost of medical care of indigent people in teaching hospitals; the cost of such professional care provided by members of medical-school faculties is estimated at $110,000,000 a year. Such a sum would go far toward ending the current deficits involved in good medical education.

The strong trend toward the use of tax money to amplify and expand medical education also receives comment: "When the public is better informed regarding the medical schools, it can decide whether to support them directly or through taxation methods." Thus, the need continues for greater effort to inform the public concerning the real issues at stake.[2,3]

This comprehensive and scholarly analysis made a timely appearance in print on the eve of the First International Conference on Medical Education, recently held in London.


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## OTITIS MEDIA AND MYRINGOTOMY

Elsewhere in this issue of the *Journal* Zonderman discusses the importance of myringotomy in otitis media and deprecates the occasional practice of allowing the eardrum to rupture spontaneously. He states it to be the consensus of leading otologists that the most effective measure in the prevention of otitic complications and chronicity is a properly performed myringotomy early in acute suppurative otitis media coupled with adequate dosage of the proper antibiotic agent as determined by culture after myringotomy.

No one will take issue on the matter of adequate dosage of the proper antibiotic — and the unfortunate results of undertreatment at early stages of the disease as illustrated by the course of the two patients described by Zonderman. More difference of opinion may exist regarding the necessity for routine myringotomy and culture for otitis media even when diagnosed and treated early in the course of infection; the difficulty in settling this important point lies in the paucity of scientific data bearing on the subject. Few would condone such sketchy therapy as was administered in the 2 cases cited. The question of the relative importance of myringotomy as compared with antibiotics is another matter. If the two procedures are held to be almost equally important the only way the question can be answered is by a suitably planned series of cases. The point cannot be decided by opinions or case reports isolated from the natural history of disease in the particular population at risk.

The fact is that the practitioner has seen such excellent results with conservative, early and ade-

quate antibiotic therapy that he will probably not retreat to the advocacy of myringotomy as a routine procedure unless its necessity can be demonstrated scientifically.

Such cases as are cited by Zonderman are exceptional, and proof that the danger of the chronically discharging ear has greatly lessened is to be found in the experience of the surgical clinics of large hospitals caring for pyogenic infections in general and such complications as otitis media in particular. For example, at the Haynes Memorial Hospital in Boston the number of mastoidectomies per year is recorded for the twenty-five-year period 1925–1950 as follows:

| | |
|---|---|
| 1925 — 28 | 1940 — 42 |
| 1926 — 26 | 1941 — 53 |
| 1927 — 38 | 1942 — 25 |
| 1928 — 37 | 1943 — 52 |
| 1929 — 22 | 1944 — 33 |
| 1930 — 49 | 1945 — 6 |
| 1931 — 45 | 1946 — 1 |
| 1932 — 55 | 1947 — 0 |
| (1933–37 figures are missing) | 1948 — 2 |
| 1938 — 59 | 1949 — 0 |
| 1939 — 29 | 1950 — 1 |

This marked drop in the necessity for surgical intervention since the antibiotics — and penicillin especially — became available is general experience all over the country. The sudden drop in mastoidectomies from 1945 on is apparently due to the use of those drugs, and the role of myringotomy in this phenomenon remains scientifically undetermined.

## TWELFTH POSTGRADUATE ASSEMBLY

The annual intensive course of the New England Postgraduate Assembly will be held this year on November 2, 3 and 4 at the Hotel Statler in Boston, with Dr. Frank P. Foster as general chairman and Dr. Charles S. Davidson as program chairman. The schedule, for the first time filling three full days, will include, in addition to the usual features, a clinicopathological conference and a larger number of clinics and panels.

Under the management of the Committee on Postgraduate Assembly of the Massachusetts Medical Society, the Assembly represents all the New England state medical societies. As in previous years the program, which appears elsewhere in this issue of the *Journal*, offers items of interest not only to those concerned with particular specialties but also to general practitioners. These conferences, symposiums, clinics and panels have each year set a new standard in postgraduate medical education. It is confidently expected that this year the courses will meet with the usual enthusiastic response from physicians all over New England.

*The young lady who has been in a somnolent state for over a month, at Harrisonburg, Va., died on Thursday last. The physicians pronounced it a paralyzation of the stomach.*

Boston M. & S. J., *October 19, 1853*

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

Ewing — George W. Ewing, M. D., of Peabody, died on September 22. He was in his seventy-sixth year.

Dr. Ewing received his degree from Baltimore University School of Medicine in 1899. He was a member of the staffs of the Thomas Hospital, Peabody, the Essex Sanatorium, Middleton, and the North Shore Baby Hospital, Salem, and was a fellow of the American Medical Association.

He is survived by his widow, a daughter, a son, five brothers and a sister.

Layton — Roy W. Layton, M.D., of Melrose, died on September 25. He was in his sixty-sixth year.

Dr. Layton received his degree from the University of Kansas School of Medicine in 1913. He was formerly secretary of the Middlesex East District Medical Society, and was president-elect at the time of his death and was a member of the Council of the Massachusetts Medical Society from 1951 to 1953.

He is survived by a daughter.

Phaneuf — Louis E. Phaneuf, M.D., of Boston, died on September 20. He was in his seventieth year.

Dr. Phaneuf received his degree from Tufts College Medical School in 1913. He was formerly surgeon-in-chief, Department of Gynecology, Carney Hospital, and was professor of gynecology, emeritus, Tufts College Medical School. A member of the staffs of the Massachusetts Women's, Newton-Wellesley, Faulkner, Beth Israel and Mount Auburn hospitals, he was a fellow of the American Medical Association and the American College of Surgeons, and was a member of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, the American Gynecological Society, the New England Obstetrical and Gynecological Society, the American Radium Society, the International Society of Surgery, the American Board of Obstetrics and Gynecology, the Boston Surgical Society, the Royal Society of Gynecology and Obstetrics of Belgium and the Gynecological Society of Romania. Dr. Phaneuf had received the Alumni Distinguished Service Award from Tufts College and was made an Officer of the Order of the Crown by King Leopold of Belgium.

He is survived by his widow, three brothers and a sister.

PAVLO — Samuel G. Pavlo, M.D., of Malden, died on September 26. He was in his seventy-first year.

Dr. Pavlo received his degree from Tufts College Medical School in 1911. He was a member of the staff of the Melrose Hospital, a charter member of the New England Obstetrical and Gynecological Society, a fellow of the American Medical Association and a former president of the Malden District Medical Society.

He is survived by his widow, a son, a daughter and three grandchildren.

## CORRESPONDENCE

### BERNARDINO RAMAZZINI

*To the Editor*: The editorial on Bernardino Ramazzini, "father of industrial medicine," in the May 21 issue of the *Journal* brought auspiciously to the notice of your readers a man already well known to dermatologists of today. He may be read, with considerable profit, by anyone interested in medicine of the seventeenth and eighteenth centuries as well as by those interested in industrial diseases. One paragraph from Ramazzini's preface to his *De Morbis Artificum*, could be appropriately incorporated into any course in public relations to students or practitioners of medicine today:

> When a physician is called to visit one of the meaner sort of people I would advise him not to feel the pulse as soon as he comes into a room without inquiring into the circumstances of the patient, nor to stand, as it were, in a transient posture to prescribe, where the life of a man is concerned; but to sit down by the patient, let the place be never so sorry, and carefully interrogate him upon such things as both the precepts of our Art and the offices of humanity require us to know.

He possessed not only noble and deeply discerning principles, but also a sly, mischievous sense of humor; the following paragraph from his famous chapter, "Of the Diseases of LEARNED MEN," is expressed with shrewd wit, combined with charm:

> I have often wondered how it came to pass, that, when epidemical diseases, such as malignant fevers, pleurisies, and other popular sicknesses, were raging all about, the practitioners of physic escaped free by a certain privilege as if it were tacked to their profession: And upon mature consideration, I am of the opinion, this good luck is owing to their caution, to their great exercise, [he has previously mentioned that physicians are constantly "walking and running about"], and to the chearfulness of their mind, when they return with full pockets from visiting their patients. In earnest, I never observed the physicians to be so much out of order, as when nobody else is sick: And this I have seen verified in a particular manner these last five years, which have been very healthy, without the appearance of any epidemical distemper. However, physicians do not always escape with impunity....

No wonder that, at the age of sixty-seven he was offered, and accepted, the chair of Practical Medicine at Padua and that the Viennese Academy accorded him the name of Hippocrates III!

BERNARD APPEL, M.D.

Lynn, Massachusetts

### ON BOOK NOTICES

*To the Editor*: Having been a steady reader of the *Journal* for three years, I wonder if you would mind the effrontery of my discussing what I consider to be a cancer in your journal's body: the "Books Received" section.

Each issue comes with a nicely manageable number of carefully written reviews and original reports, highly spiced with the Case Records and the delightful Doctors Afield. Then, hanging in the rear is what can be considered at best to be the editorial equivalent of a ponderous, 20-pound lipoma; I have biopsied this mass for three years: it is indisputably anaplastic.

A typical listing includes a sentence or two of identification, often useless once the title is read, a description of how the text is divided, how many men collaborated, and the fact that the book is up to date (the presumption of its newness we are not allowed to make), with a note on the quality of the paper, the clarity of the type face, the length of the index and the fact of bibliographies. The vast majority of the reviews close with the wonderfully dull thud, "The book should be in all collections on the subject," or its equivalent.

These facts are of some importance, but the usual situation is that they are all the facts we receive. To me, such a review in a publication of your character is worse than useless; often these cells occupy two and three pages, amply fulfilling the criterion of indiscreet growth.

How much better it would be to have a few carefully written, signed reviews of the major publications! Certainly the collective medical genius of Boston would respond handsomely to such an effort, particularly if recompensed with a gratis copy. A medical book review should always embody one definite evaluation: the place of the book in the general medical literature. Perhaps you think that these are not reviews, but "Listings." If so, I believe "Books Received" should get several thousand editorial r and be replaced with a stimulating review section put on a par with the rest of the *Journal*.

What the average reader wants to know, I think, is what the best of the new books are, and how they rank in their fields. Certainly, a review of one column by Dr. Dameshek of the third edition of Wintrobe's *Hematology* would be far more pleasant and stimulating than the dull listing of *A Student's Radiological Mathematics*. The important points of dispute should be brought forth, but please not in the style of the *Journal of the American Medical Association*, with its usual "One finds the thyroidea ima labelled incorrectly on page 878."

JOHN M. BUDINGER, Senior
Northwestern University Medical School

Chicago

## BOOK REVIEWS

*The Superego: Unconscious conscience — the key to the theory and therapy of neurosis.* By Edmund Bergler, M.D. 8°, cloth, 367 pp. New York: Grune and Stratton, 1952. $6.75.

Dr. Bergler, in this readable and thought-provoking treatise, extends and reinterprets the theories expressed in his earlier publications. He clearly aligns his thinking with that of Freud and the psychoanalytical school, using as a springboard the "fixed" theory of the dynamic unconscious and emphasizing the complexities of the self-punitive superego, the "unconscious conscience." The importance of this inner demon, so diabolically active in the neurotic person, he believes, has been inadequately stressed and naïvely conceived: "...any attempt at a theory and therapy of neurosis is out of focus unless the superego, and the most important defense of the unconscious ego, created to escape the latter's tyranny — the defense of the orally based masochism — are put in the center."

Much of the neurotic's faulty construction of his reality is conceived as predating the Oedipal situation emphasized by Freud. The child is born with libido and aggression, which charge its megalomania to form an ego ideal — a magic-shrouded life goal. Because this goal cannot be achieved (who becomes what he once dreamed he would be?), the aggression is turned outward for narcissistic pleasure and inward (Thanatos), forming a taunting inner voice reprimanding one for failure — for Diamonion. Since the ego ideal is formed from the infant's megalomania and the introjected parent images, the oral conflict solution becomes of utmost importance for setting a pattern of future behavior in emotional situations. Most so-called normal people solve this conflict with well known sublimations and substitutions, leaving a minimal residue of anxiety but nevertheless obvious evidence of this oral struggle. Neurotics fail to resolve this phase and arrive at a masochistic solution fomenting the Diamonion of their inner judge, the superego.

The author cites many fascinating case examples to illustrate the five-layer structure behind conflict situations. "Orally based psychic masochism" (Layer I) is presented as the basic problem in each. A second defense (often neurotic aggression), Layer III, is offered instead of the basic defense, which has been vetoed by the superego. This defense is again vetoed, and another symptom complex is offered as a substitute solution. Analysis often only uncovers the third conflict, Layer V, and merely suspects the pseudoaggression of the second defense, Layer III. Failing to point out the basic masochism, the analysis is foiled by the neurotic palimpsest.

Early in the discussion, the author points out that the inner conscience forces the ego to accept a "lesser crime" rather than to admit to the aggressions of the oral phase. This is not to be misconstrued as a legal term, indicating a lessening of the quantity of self-punishment. The original problem is merely distorted to make a more acceptable theme to present to the world of awareness. Thus, for example, the voyeurist becomes an exhibitionist, failing to suppress the desire to peep while giving lip service to the exhibitionism, the "lesser crime."

A large measure of psychic energy is expended to "ward off the constant avalanche of torture" emanating from the superego. "Man's inhumanity to man is equaled only by man's inhumanity to himself."

The material will be of special interest to those specializing in the field of psychiatry but will be theoretically complex for the lay reader. This book, based on Dr. Bergler's long and obviously keen observations of his cases, cannot be too highly recommended.

JOHN E. WRIGHT, M.D.

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*Gynecology: Diseases and minor surgery.* Compiled and edited by Robert J. Lowrie, M.A., D.D., D-OG. With a foreword by Claude E. Heaton, M.D. 4°, cloth, 806 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1952. $22.50.

This monumental work represents the culmination of many years of effort and preparation on the part of many minds under the able editorship and supervision of Dr. Robert J. Lowrie, of New York University. This first volume alone, dealing entirely with the diseases and minor surgery of gynecology, consists of 800 pages in 53 chapters, and is lavishly and superbly illustrated with 775 figures, of which 19 are in colors. Moreover, each chapter is a monograph in its own right, and follows a standard pattern of presentation, preceded by a summary and followed by an ample bibliography. There is an admirable descriptive foreword by Dr. Claude E. Heaton, also of New York University.

Among the 79 contributors from 30 medical schools and other institutions in the United States, Canada and England, one is particularly pleased to note in this volume the names of four well known Boston gynecologists, Drs. Boland, Gorman, Meigs and Pemberton. A second volume, devoted to major and minor gynecological surgery, is promised in the near future. Its advent will be awaited with the most interested anticipation by general practitioners and surgeons alike.

ROBERT M. GREEN, M.D.

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## BOOKS RECEIVED

**The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.**

*Expert Committee on Insecticides.* Third report. 8°, paper, 36 pp. Geneva: World Health Organization, 1952. $0.25. (World Health Organization Technical Report Series No. 46.)

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*Die Krankheiten der endokrinen Drüsen unter Berücksichtigung ihrer Anatomie und Physiologie.* By Prof. Dr. Hermann Zondek. With the collaboration of Hannah E. Leszynsky and Gerda Wolfson-Zondek. 8°, cloth, 799 pp., with 188 illustrations. Basel: Benne Schwabe and Company, 1953. Geb. Fr. 72.-

Dr. Zondek, an eminent authority in the field of endocrinology, now lives in Jerusalem. His book has an interesting history. It was first published in 1923 with frequent editions in German up to 1948, and has been translated into English and French. It has now been revised and brought up to date. The material is divided into two parts, general and special. The first part, numbering 200 pages, is devoted to the anatomy, physiology and chemistry of the organs of internal secretion. The second part, comprising 544 pages, deals with the diseases of the various endocrine organs. Short lists of references are appended to the various chapters; there is an extensive index, and the publishing is excellent. The book is outstanding, and is recommended to all persons interested in endocrinology and to medical libraries.

*Cancer in Man.* By Sigismund Peller, M.D. 8°, cloth, 556 pp., with 24 illustrations and 85 tables. New York: International Universities Press, Incorporated, 1953. $12.00.

Dr. Peller reviews the present status of cancer and its control. He evaluates the literature on the basis of a bibliography of 25 pages. The text is divided into three parts: the pathology of human cancer, epidemiology and cancer control. He discusses control based on old concepts and presents his own new theory. There are indexes of authors and subjects. The book should be available to all persons interested in cancer.

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*Therapeutische Technik für die ärztliche Praxis.* By various specialists. Edited by Prof. Dr. Karl Hansen. Third revised edition. 4°, cloth, 985 pages, with 695 illustrations. Stuttgart: Georg Thieme, 1952. DM 89.- (Distributed by Grune and Stratton, New York.)

This composite book on treatment is similar to American books of the same type. It was first published in 1906. The present, revised edition is the joint work of 18 German physicians. The text is divided into two parts on general and special treatment. The physical methods and the use of drugs in general including a chapter on psychology in handling the sick person, are discussed in the general part. The special part deals with the special methods used in internal medicine and neurology, pediatrics, orthopedics, genitourinary disease, gynecology and obstetrics, conditions of the ear, nose and throat and eye, stomatology and special surgery. The final chapter is on psychotherapy. There is an extensive index, and the publishing is excellent as in most Thieme books.

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*Die Angiographie zur Erkennung, Behandlung und Begutachtung peripherer Durchblutungsstörungen.* By Dr. Med. Habil. H. W. Pässler, chief city physician and physician-in-chief, Städt. Krankenhauses Leverkusen. 4°, paper, 115 pp., with 102 illustrations. Stuttgart: Georg Thieme, 1952. DM 29.70. (Distributed by Grune and Stratton, New York.) (*Fortschritte auf dem Gebiete der Röntgenstrahlen Vereinigt mit Röntgenpraxis. Archiv und Atlas.* Ergänzungsband 67.)

This monograph discusses the value of angiography in the diagnosis and treatment of disorders of the peripheral blood vessels.

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*Second Annual Report on Stress.* By Hans Selye, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada), professor of experimental surgery and director, Institut de Médecine et de Chirurgie expérimentales, Université de Montréal; and Alexander Horava, M.D. (Lausanne), research associate and librarian, Institut de Médecine et de Chirurgie expérimentales, Université de Montréal. 8°, cloth, 526 pp., with illustrations. Montreal: Acta, Incorporated, 1952. $10.00.

This report is the second in a projected series of annual supplements to *Stress*, written by Dr. Selye in 1950. The literature for 1951 is reviewed, and over 4000 publications are noted, although many borderline subjects have been eliminated. The text is divided into two parts on general and special physiology and pathology. There is an atlas of 16 plates. The bibliography, which is arranged by authors alphabetically, comprises 174 pages. The book is an essential reference tool for medical librarians and of special value to biologists and endocrinologists.

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*New and Nonofficial Remedies: Containing descriptions of the articles which stand accepted by the Council on Pharmacy and Chemistry of the American Medical Association on January 1, 1953.* Issued under the direction and supervision of the Council on Pharmacy and Chemistry, American Medical Association. 12°, cloth, 623 pp. Philadelphia: J. B. Lippincott Company, 1953. $2.65.

Before the publication of this volume, *New and Nonofficial Remedies* was made up of two sections, one comprising general statements and monographs describing actions, uses and dosages of various drugs and the other the tests and standards for Council-accepted drugs for which official standards are not available. Henceforth this material will appear in two separate volumes, *New and Nonofficial Remedies* (including the bibliography of unaccepted products and an index to distributors) and *Tests and Standards for New and Nonofficial Remedies.* The decision to split the material was made after a survey revealed that the two parts were used by two different groups, physicians and pharmacists. The text has been brought up to date. The book is an essential reference tool for all medical libraries.

## NONCLINICAL NOTES

Dr. Shields Warren, pathologist for the New England Deaconess Hospital and director of the Deaconess Cancer Research Institute, has been elected chairman of the Executive Committee of the Boston University Board of Trustees.

## NOTICES

### ANNOUNCEMENT

Dr. Arnold Starr announces the removal of his office from 520 Beacon Street to 416 Marlboro Street, Boston, for the practice of surgery.

Dr. David Weintraub announces the removal of his office to 311 Commonwealth Avenue, Boston.

### KENNETH D. BLACKFAN MEMORIAL LECTURE

The Kenneth D. Blackfan Memorial Lecture will be given by Dr. Reginald Lightwood, director, Paediatric Unit, St. Mary's Hospital Medical School, London, and visiting physician-in-chief, Children's Hospital, Boston, on Tuesday, October 27, at 5 p.m. in the auditorium of the Jimmy Fund Building, 35 Binney Street, Boston. The topic will be "The Clinical Features of Idiopathic Hypercalcemia in Infants."

### BOSTON LYING-IN HOSPITAL JOURNAL CLUB MEETINGS

The Journal Club of the Boston Lying-in Hospital announces the following meetings, open to interested physicians and medical students, to be held in the Boston Lying-in Hospital auditorium, from 4 to 5 p.m.:

October 23. Dr. Edward Meilman. The Mechanism of Action of the Hypotensive Drugs in Toxemia of Pregnancy.
November 6. Dr. George O. Bell. Hyperthyroidism in Pregnancy.
November 20. Dr. John W. Strieder. The Effect of Surgical Lesions of the Chest on Pregnancy.
December 4. Dr. J. Hartwell Harrison. The Significance of Urinary Infection in Pregnancy and the Post-partum Period.
December 18. Dr. John C. Laidlaw. Virilism in the Female.

Coffee will be served at 3:45 p.m.

### MASSACHUSETTS MEDICO-LEGAL SOCIETY

The fall meeting of the Massachusetts Medico-Legal Society will be held in the George Burgess Magrath Library, Harvard Medical School, Building E 1, on Wednesday, October 21, at 2:30 p.m. Dr. Francis H. Carr will speak on the subject "Medicolegal Aspects of the Worcester Tornado."

### AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The next scheduled examination (Part 1), written examination and review of case histories, for all candidates will be held in various cities of the United States, Canada, and military centers outside the continental United States, on Friday, February 5, 1954.

Case abstracts are to be sent by the candidate to the Secretary, Robert L. Faulkner, M.D., 2105 Adelbert Road, Cleveland 6, Ohio, as soon as possible after receiving notification of eligibility to the Part 1 written examination.

Candidates are reminded that application for re-examination in Part 2 must be made before February 1 of any year.

### SOCIETY MEETINGS AND CONFERENCES

October 14–December 2. Course in child psychiatry (pediatric neuropsychiatry). Page 428, issue of September 3.

October 17–20. American Association of Blood Banks. Page 1126, issue of June 25.

October 19 and 26, November 2 and 9. Fried Lectures. Page 634, issue of October 8.

October 19–30. New York Academy of Medicine. Page xvii, issue of June 11.

October 19–December 21. Hartford Medical Society Program. Page 260, issue of August 6.

October 20. Harvard Medical Society. Page 634, issue of October 8.

October 20. South End Medical Club. Page 634, issue of October 8.

October 20. Middlesex South Woman's Auxiliary. Page 634, issue of October 8.

October 21. Fifth Conference on Alcoholism. Page 634, issue of October 8.

October 21. Massachusetts Medico-Legal Society. Notice above.

October 21–23. International Symposium on Virus Infections. Page 546, issue of September 24.

October 23 and 24. Eastern Section of American Trudeau Society. Page 506, issue of September 17.

October 23–December 18. Boston Lying-in Hospital Journal Club. Notice above.

October 25–29. American Institute of Dental Medicine. Page 124, issue of July 16.

October 27. Hampden District Medical Society. Page 634, issue of October 8.

October 27. Kenneth D. Blackfan Memorial Lecture. Notice above.

October 28. New England Obstetrical and Gynecological Society.

October 28. Phi Delta Epsilon Graduate Club of Boston. Page 634, issue of October 8.

November 2–4. New England Postgraduate Assembly. Hotel Statler, Boston. Page ii, issue of October 8.

November 6 and 7. American College of Cardiology. Page 506, issue of September 17.

November 12–14. Annual Convention of the National Society for Crippled Children and Adults. Chicago.

November 18. Massachusetts Society of Examining Physicians. Page 546, issue of September 24.

November 19 and 20. Inter-Society Cytology Council. Page 170, issue of July 23.

December 6. American Academy of Dental Medicine. Page 170, issue of July 23.

May 31–June 3, 1954. American Urological Association. Page xvii, issue of July 23.

September 12–15, 1954. Second International Congress of Cardiology. Page 44, issue of July 2.

September 16–18, 1954. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

### District Medical Societies

**HAMPDEN**

October 27. (Combined with the Auxiliary.) Roger Smith Hotel, Holyoke. 6:00 p.m.

**MIDDLESEX EAST**

November 18.
January 20. (Combined with the Auxiliary.)
March 24.
May 12. Annual Meeting. (Harlow Dinner.)

**MIDDLESEX SOUTH**

October 20. Woman's Auxiliary. The Meadows, Framingham. 1:00 p.m.

### Calendar of Boston District for the Week Beginning Thursday, October 22

Thursday, October 22

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

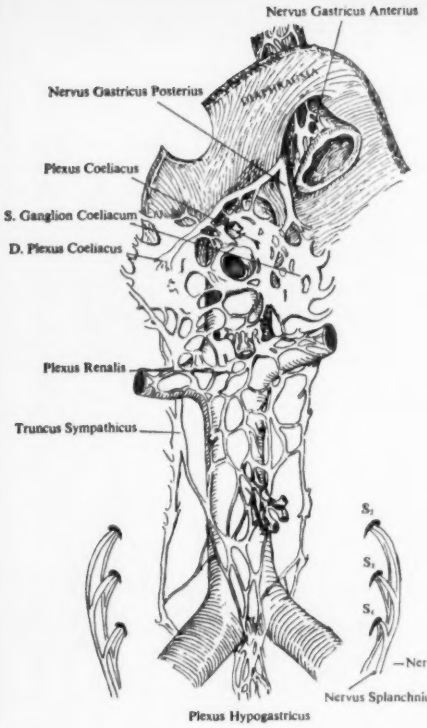
12:00 m.–1:00 p.m. New England Center Hospital Conference. Benign Disorders of the Esophagus. Dr. Franz J. Ingelfinger. Stearns Auditorium, New England Center Hospital.

4:00–5:00 p.m. Combined Seminar. CRI and Children's Hospital. Testicular Radiation. Dr. Lloyd Fogg. Transplantation of Human Tumors. Dr. Alfred Handler. Joslin Auditorium, New England Deaconess Hospital.

*4:30–5:30 p.m. Electrolyte balance in renal disease. Dr. E. Hinton. Nurses' Home, Cambridge City Hospital.

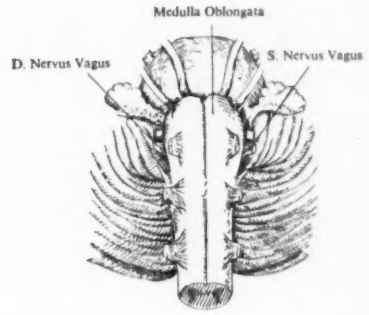
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

(*Notices concluded on page xxi*)




*Abdominal autonomic plexus (sympathetic)*

*Central origin of the vagus nerves (parasympathetic)*

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"The need[1] for suppressing gastric motility and spastic states is . . . fundamental in peptic ulcer therapy. Since the cholinergic nerves are motor and secretory to the stomach and motor to the intestines, agents capable of blocking cholinergic nerve stimulation are frequently used to lessen motor activity and hypermotility."

Banthīne[2] "has dual effectiveness; it inhibits acetylcholine liberated at the postganglionic parasympathetic nerve endings and it blocks acetylcholine transmission through autonomic ganglia."

It has been shown[1] to diminish gastric motility and secretion significantly as well as intestinal and colonic motility.

The usual schedule of administration in peptic ulcer is 50 to 100 mg. every six hours, day and night, with subsequent adjustment to the patient's needs and tolerance. After the ulcer is healed, maintenance therapy, approximately half of the therapeutic dosage, should be continued for reasonable assurance of nonrecurrence.

Banthīne® (brand of methantheline bromide) is supplied in: Banthīne ampuls, 50 mg.—Banthīne tablets, 50 mg.

It is accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

1. Zupko, A. G.: Pharmacology and the General Practitioner, GP 7:55 (March) 1953.

2. McHardy, G. G., and Others: Clinical Evaluation of Methantheline (Banthīne) Bromide in Gastroenterology, J.A.M.A. *147*:1620 (Dec. 22) 1951.

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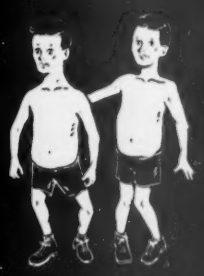
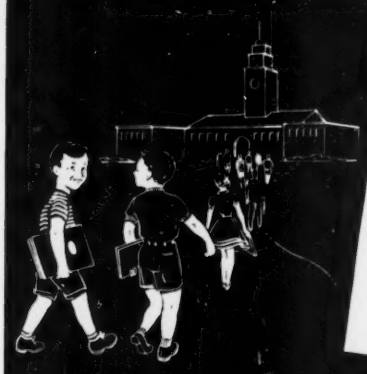
1-212A

# 50 YEARS AGO

*"... in a word, deficiency of fat in the food is one of the chief factors in the production of rickets."* (1)



# TODAY...



We know that lack of fat-soluble vitamin D in the diet is one of the major causes of rickets. Other deficiency diseases are also caused by a lack of adequate vitamins in the diet.

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**VITAMIN CONTENT PER QUART OF NORMAL DILUTION:**

| | |
|---|---|
| Vitamin A 2500 U.S.P. Units | Thiamine . 0.6 milligrams |
| Vitamin D 800 U.S.P. Units | Niacin . . . . . 5.0 milligrams |
| Vitamin C . . . . . None | Riboflavin 1.0 milligrams |

A source of vitamin C should be prescribed by the physician.

(1) Cheadle—*Artificial Feeding and Food Disorders of Infants*. Sixth Edition (1906)

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## NOTICES (*Concluded from page 672*)

FRIDAY, OCTOBER 23

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
8:00–9:00 a.m. Retinitis. Drs. William Pote and Howard F. Root. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*12:30–1:30 p.m. Burns. Dr. M. White. Ward B Classroom, Cambridge City Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
2:00–3:30 p.m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.
4:00–5:00 p.m. Journal Club Meeting. Boston Lying-in Hospital Auditorium, 221 Longwood Avenue.
4:00–6:00 p.m. X-ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, OCTOBER 24

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
8:00–9:00 a.m. Lahey Clinic Medical Conference. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, OCTOBER 26

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
12:00 m.–1:00 p.m. Medical Pathology Conference. Pratt Diagnostic Clinic, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
7:00–9:00 p.m. Combined Anesthesia Resident Training Program. Jimmy Fund Auditorium, Children's Medical Center, 35 Binney Street.
*8:30 p.m. Fried Lecture. The Diagnosis of Adrenal Insufficiency and Cushing's Syndrome. Dr. George W. Thorn. Usen Auditorium, Newton-Wellesley Hospital.

TUESDAY, OCTOBER 27

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:30 a.m.–12:30 p.m. Grand Rounds. Combined Services. Nurses' Home, Cambridge City Hospital.
*12:00 m. Regular Grand Rounds of the Pediatric Department. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
12:00 m.–1:00 p.m. Endocrine Conference. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*12:30–1:30 p.m. Medical Journal Club. Cafeteria, New England Deaconess Hospital.
*4:30–5:30 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
5:00 p.m. Kenneth D. Blackfan Memorial Lecture. Clinical Features of Idiopathic Hypercalcemia in Infants. Dr. Reginald Lightwood. (Children's Medical Center.) Auditorium, Jimmy Fund Building, 35 Binney Street.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, OCTOBER 28

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Jimmy Fund Building, 35 Binney Street.
12:00 m.–1:00 p.m. Psychiatry Conference. Dr. Hope. Stearns Auditorium, New England Center Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:30–2:30 p.m. Pathological Conference. Dr. C. Jones. Nurses' Home, Cambridge City Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. (Children's Medical Center.) Jimmy Fund Building, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
6:30–7:30 p.m. Phi Delta Epsilon Graduate Club of Boston. Cocktail and dinner meeting. Hotel Beaconsfield, Brookline.
*7:30–9:30 p.m. Lahey Clinic Lecture. Drug Therapy of Tuberculosis. Dr. Carl Souders. Drug Therapy of Blood Diseases. Dr. Donald Cyr. Joslin Auditorium, New England Deaconess Hospital.

## *Index to Advertisers*


| | PAGE |
|---|---|
| Abbott Laboratories | vi, vii, xvi |
| Ayerst, McKenna & Harrison, Ltd. | viii |
| Baker Laboratories, Inc. | xvii |
| Chester A. Baker Laboratories, Inc. | xx |
| Baldpate, Inc. | xx |
| Boston Medical Laboratory | xviii |
| Burroughs Wellcome & Co., Inc. | x |
| Ciba Pharmaceutical Products, Inc. | Back Cover |
| David Memorial Nursing Home | xx |
| Electroencephalographic Laboratory, Inc. | xviii |
| Endo Products, Inc. | xii |
| Jack Fadden and Peter Provinzano | xx |
| Fellows Medical Mfg. Co., Inc. | xiii |
| Federated Accounting Services, Inc. | xviii |
| Glenside, Inc. | xx |
| Hanover House, Inc. | xx |
| H. P. Hood & Sons | ix |
| Lakeside Laboratories, Inc. | v |
| Leary Laboratory | xviii |
| Lederle Laboratories | After iv |
| Eli Lilly and Company | xiv |
| Mason Drug Company | xix |
| Medical Clearing Bureau, Inc. | xix |
| New England Postgraduate Assembly | iv |
| Parke, Davis and Company | ii, iii |
| Perkins School | xx |
| Charles Pfizer & Co., Inc. | xi |
| Ring Sanatorium | xx |
| W. B. Saunders Company | Front Cover |
| G. D. Searle and Company | xv |
| Southern Medical Supply Co. | xix |
| Storrow House (Massachusetts General Hospital) | xviii |
| United States Brewers Foundation, Inc. | xiii |
| Washingtonian Hospital | xx |
| Wiswall Sanatorium | xx |
| Woodside Cottages, Inc. | xx |

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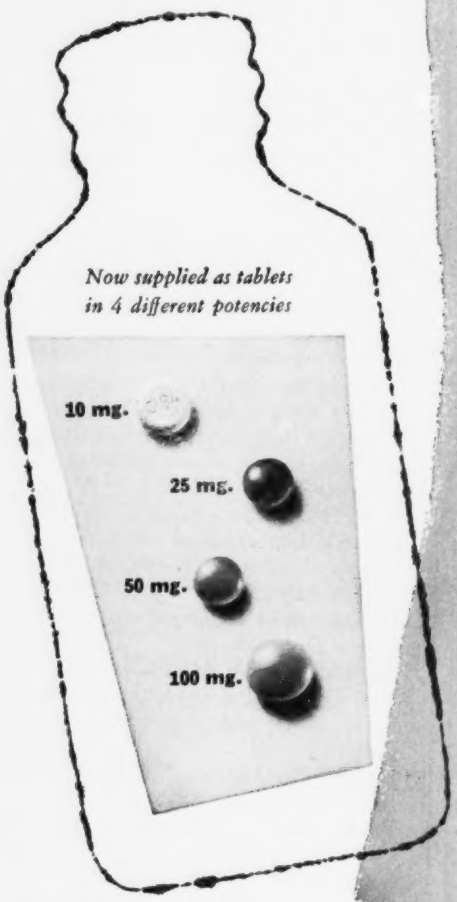


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